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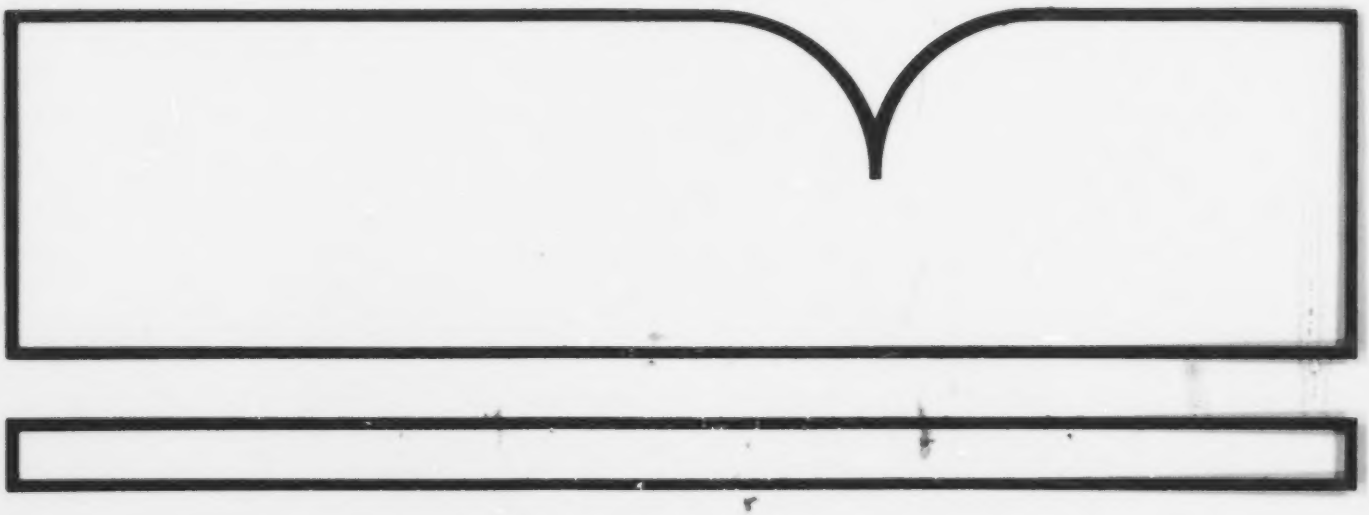

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16. ABSTRACT

It is apparent that high-level lead exposure can have serious effects on the intellectual and behavioral development of young children. Furthermore, substantial numbers of children are at risk for lead exposure. However, current concerns revolve more around low-level chronic exposure than around high-level lead poisoning. Of particular concern are issues of quantification of behavioral toxicity, dose-response parameters associated with toxicity, and critical periods of exposure; i.e. what types of behavioral of intellectual deficits occur at what levels of lead exposure during various stages of development. The present review attempts to organize the very large human and animal behavioral literature which has evolved during the past 10 to 15 years.

The review is organized into two major sections: Part I, a clinical review which will examine only those studies relevant to the issue of behavioral effects resulting from relatively low-level chronic exposure, and Part II, a review of animal studies which will focus on behavioral reports only; i.e. studies where the dependent variable is learning, performance, or some aspect of locomotor behavior. No attempt will be made to review the equally large animal literature dealing with physical development, neurochemical, electrophysiological, or neuropathological endpoints of toxicity.

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BEHAVIORAL EFFECTS OF MODERATE LEAD EXPOSURE IN CHILDREN AND ANIMAL MODELS: PART 2, ANIMAL STUDIES

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IV. ANIMAL STUDIES

A. Review of Animal Models

Due to the potentially serious consequences of lead exposure in children and the difficulty in coming to grips with the multitude of interacting factors evident in the human population, researchers have sought to develop an animal model(s) which would provide them with much needed experimental control. Prior to 1965, the animal literature on cerebral dysfunction resulting from lead exposure was limited, largely due to the inability to produce unequivocal neurological changes in laboratory animals comparable to human clinical cases of lead encephalopathy. Adult animals appeared to be resistant to the central nervous system (CNS) effect of lead poisoning. The major criticism of most experimental models was that very large doses of lead were required to produce even marginal toxicity and that often there was a paucity or even absence of clinical manifestations of CNS toxicity in these models. A breakthrough in the development of an experimental model exhibiting CNS morphological alterations similar in some respects to those occurring in children with lead encephalopathy occurred in 1965 when Pentschew and Garro[1] showed that lesions of the CNS of neonatal rats can be produced when lead fed to the lactating mother rat is transmitted to the suckling young via the maternal milk. It was reported that the developing neonates showed no early adverse effects of being nourished by milk containing lead, other than a profound retardation in body growth. Paralysis of the hind legs occured about 20 to 30 days after birth. It should be noted that growth retardation and paralysis are not encountered in children. The cerebellum of these animals contained numerous small petechial hemorrhages and was deeply pigmented. Abnormal vascular permeability was most striking in the corpus striatum, occipital cortex, cerebellum, and lower spinal cord. Replications of the "Pentschew" lead encephalopathy have been reported by Lampert

et al.,[2] Thomas et al.,[3] Michaelson,[4] Krigman et al.,[5] and Clasen et al.[6] in the rat, and by Rosenblum and Johnson[7] in the mouse. The characteristic histopathological brain changes produced by this form of experimental lead poisoning have enabled the study of the sequence of events that gives rise to cerebral dysfunction following lead poisoning as well as permitting the further evolution of an animal model suitable for the investigation of behavioral concomitants of lower levels of lead exposure.

Several different models have been developed for use in behavioral testing paradigms. The most common[8,9] has been a modification of the Pentschew and Garro procedure[1] wherein the level of exposure to the dam is reduced below that which causes paraplegia. Usually the lead is added to the drinking water rather than the food in order to facilitate estimation of dosage and prevent contamination of the animal quarters by powdered lead salts. In this model the pregnant and/or lactating dam again serves as a vehicle for transmission of low quantities of lead from her drinking water to the fetus and/or through her milk to the suckling. By employing maternal blood and milk as the vehicle, it is possible to obtain a relatively continuous early exposure. The principal disadvantage of employing the lactating dam as a vehicle for lead administration to sucklings is the potential for unintended alteration in the quantity or quality of milk production or maternal behavior. A further discussion of methodological problems associated with this model is available.[10]

Because of the latter-mentioned disadvantages, some investigators have chosen to administer lead directly to the neonate via oral intubation.[5] However, this technique has its own inherent disadvantages, including (1) delivery of a single bolus of the agent with a relatively short transit time through the gastrointestinal tract, (2) large periodicity in resultant blood-lead concentrations, (3) trauma associated with daily forced feeding, and (4) considerable expenditure of time and effort by a skilled technician in order to produce a large test population.

Several researchers[11,12] have chosen to employ a continuous multigenerational exposure protocol modeled after standard Phase I teratogenicity screening protocols.[13] Lead exposure is initiated in the parental generation about 60 days prior to mating and the exposure continues throughout gestation, lactation, and into the adulthood of the offspring. Such procedures produce a complex pattern of route and level of exposure to the offspring and mask the determination of critical periods of exposure. However, as an initial screening procedure, this methodology more closely models current areas of concern; i.e., chronic low-level exposure from multiple sources throughout all periods of development.

The early success with rodent models as well as a growing awareness of some of their disadvantages has led investigators to explore the utility of other neonatal models, e.g., neonatal rabbits[14] and infant rhesus monkeys.[15] However, it is too soon to evaluate the utility of these latter models. None of the investigators concerned with examination of neurobehavioral effects have explored the utility of an inhalation exposure route.

Finally, there have been repeated attempts to develop adult animal models. Species chosen have included the sheep,[16] guinea pig,[17] weanling and adult rat,[18] and pigeon.[19] With the exception of the recent work with adult guinea pigs[20,21] these attempts have been largely unsuccessful (see Table 1). In the guinea pig model of acute lead encephalopathy, seizures and death are regularly produced after five daily oral doses of 155 mg/kg of lead carbonate. Bouldin and Krigman[22] contend that the acute onset of seizures and the paucity of CNS morphologic alterations seen in this model resemble more closely the disease in man than the acute encephalomyelopathy produced in suckling rats. Unfortunately the use of this model has been limited to neurophysiological and neuropathological studies with no behavioral studies to date. This is no doubt due

Table 1
BEHAVIORAL INVESTIGATIONS USING ADULT ANIMAL MODELS

Species	Age	Task	Finding	Ref.
Rat	21—35 days	Water T-maze	No effect	52
	Weanling and adult	Hebb-Williams maze	No effect	18
	Adult	T-maze	No effect	58
	Weanling	FI-30	Altered performance	47
Mouse	Adult	Water Y-maze	Decreased performance*	55
	Adult	Water T-maze	No effect	57
Sheep	Adult	Auditory signal detection	Decreased performance	16
Pigeon	Adult	FR 30-FI 5 min	Variable performance*	19
	Adult	Serial position	Decreased performance	71

*Effects were seen in the presence of overt signs of lead toxicity.

to a limited experience with behavioral testing of guinea pigs. However behavioral evaluation is not impossible and should be encouraged.

B. Potential Utility of Animal Models

As mentioned previously, the utility of an animal model arises from the control and manipulative power it provides to the investigator. But what should be controlled? What are the principal questions to be posed? What data would be most useful to resolution of the clinical problem? Finally, how well can the animal data be extrapolated to man? These are difficult questions and there is no universal agreement on the answers. However, the following is an attempt to indicate some of the issues which could be explored through animal models. This will in turn provide a frame of reference against which we can evaluate the animal studies conducted to date.

In addition to the behavioral parameters, commonly employed clinical indices of lead exposure, such as alterations in hematocrit, hemoglobin concentration, erythrocytic protoporphyrin, blood lead levels, urinary δ-amino levulinic acid concentration, and urinary lead levels in response to diagnostic chelation could be monitored in the animal model. This would provide a common frame of reference between the human and animal studies. Furthermore, it would permit a comparison between dose-response and temporal relationships of these better-known indices of toxicity and behavioral, neurochemical, or neurophysiological indices of toxicity.

Studies could be undertaken to establish critical periods, levels, and durations of exposure which produce reliable changes in behavior. It would be helpful to know the earliest time point, relative to exposure, at which reliable behavioral changes can be demonstrated and the temporal extent to which behavioral effects persist beyond termination of exposure.

There are marked differences in the degree to which children react to apparently equivalent body burdens of lead. Does similar individual variation in susceptibility exist in animals? If so, it would be of value to identify those clinical indices of exposure, exposure history, or some constellation of pre-exposure variables which best predict the subsequent susceptibility of individual animals to the behavioral toxicity of lead.

There have been a number of observations which suggest that other environmental or genetic factors might interact with lead exposure to produce neurobehavioral deficits. Interaction studies could be carried out with an animal model. For example, it would be possible to examine the interactive effects of "developmental stress" by rearing rodents in oversized litters. This would produce a spectrum of growth rates within the litter brought about by competition for food and maternal care. The relative sensitivity of these littermates to concurrent lead exposure could then be examined. Interaction studies employing more specific nutritional deficits, e.g., low calcium or iron, might also be undertaken.

Finally, it is necessary to address the issue of extrapolation of behavioral data derived from "lower" mammals to man. What are the implications for man of a confirmed lead-related behavioral deficit in an animal model? Let us first focus attention on the fact that behavioral testing paradigms require that the animal interact with its environment. This "environment" may be simple or complex, artificial or natural, relatively unchanging or rapidly changing. Likewise the behavior being quantitated may be innate, acquired, sex dependent, specific to a particular species, or common to all mammals. Behavorial toxicity testing paradigms are intended to assess how a well-defined group of animals interacts with an equally well-defined enviroment and more importantly to establish what changes occur in the nature of this interaction during or following exposure to a toxin such as lead. A difference between the observed behavior of treated and control animals indicates that the treatment has altered how the test animal perceives and responds to its environment. It is unlikely that the mechanism responsible for the change in behavior will be immediately clear. More likely the cause will become evident only after more specialized behavioral, biochemical, and physiological testing.

In the situation just described, the interest is not in the specific behavioral alteration, but rather in the use of that alteration as an observable index of toxicity which can be used to establish dose-response and threshold relationships. The more difficult issue in extrapolation from lower animals to man arises from attempts to predict the presence of isomorphic behavioral changes in man based on specific behavioral effects observed in animals. Thus, we see reports wherein an increase in locomotor activity of lead-exposed animals in novel environments is termed "hyperactivity" and parallels are drawn between this behavior and the complex syndrome of "childhood hyperkinesis". Such generalizations, without qualification, represent an unwarranted extrapolation and misuse of the data.

The issue of extrapolation or cross-species generalization is an old one in the field of neuropsychology. Warren and Kolb,[21] in a recent treatment of this issue, have drawn a distinction between species-specific behaviors, which have been selected through evolution to promote survival of the species in a unique niche, and class-common behaviors which are demonstrable in all mammals. Thus, each mammalian species has a unique behavioral repertory yet shares some behavioral traits and capacities with all other mammals. For example, all mammalian mothers provide milk and maternal care. All mammals learn operant behaviors under complex schedules of reinforcement. Finally, we might note that all mammals must localize sounds accurately and have evolved neural circuits to mediate sound localization; this is class-common behavior. How an animal responds to the sound, i.e., approach, flight, or freezing behavior, is determined by whether it is a predator or a possible prey and by other characteristics of its species. Thus, the response is species-specific.

A further consideration of the problems every mammal must solve if it is is to survive will suggest those behaviors most likely to be mediated by common neural substrates. All mammals must detect and interpret sensory stimuli, relate this information to past

experience, and act appropriately. The behavioral evidence indicates that these functions are carried out in qualitatively similar ways when animals are observed under neutral conditions, i.e., in the absence of stimuli significant only for a particular species. Thus, in order to enhance direct extrapolation of behavioral data to other species, one might first focus on the evaluation of class-common behaviors.

C. Methods of Behavioral Assessment

1. Definition of Learning and Performance

The scope of behaviors which come under the general rubric of learning and performance is quite broad. The methods used to quantitate these behaviors is even broader. Generally the term "learning" applies to the acquisition and retention of new behavioral patterns. Thus, acquiring the ability to (1) run through a maze without error, (2) avoid a shock by making the appropriate response to a warning signal, or (3) make a discrimination between two lights of approximately equal brightness are examples of learning tasks. The ability to *acquire* and *retain* these new behavioral patterns is a trait shared by all mammals.

It should be noted that a "learning task" provides a composite measure of the functioning of the CNS. Comparable rates of learning between experimental and control groups implies comparable levels of (1) motor function, e.g., running time through a maze, (2) motivation, e.g., latency to respond to a stimulus, (3) sensory capabilities, e.g., threshold for shock, light, or sound detection, (4) memory function, e.g., a retest of performance several days after initial learning, in order to assess recall, and (5) learning, e.g., the ability to form an association between two stimuli. Thus, the detection of a difference between two groups of subjects on a "learning task" does not necessarily imply a difference in the fundamental learning process. The learning task provides a global screening measure which is usually followed by more discrete tests of the specific function thought to be affected.

Performance measures, as distinct from learning measures, quantitate previously acquired or innate behaviors. Thus, eating and drinking patterns, circadian activity patterns, balance on a rotating rod, signal detection, and maintenance of bar-pressing behavior under the control of specific schedules of reinforcement, all fall under the general rubric of "performance". Again, failure to attain or maintain a given level of performance may be indicative of a more specific underlying deficit, e.g., impaired ability to maintain attention, alteration in basic motivational levels, or deficient motor coordination.

The preceding discussion is of necessity brief and devoid of many qualifying statements. Several good texts and reviews are available for those who desire a more extensive treatment of procedures used in the experimental examination of behavior in animals.[24-27]

2. Techniques for Quantifying the Learning Process

Although, as mentioned previously, a wide range of behavioral testing procedures are available, relatively few have been used in the evaluation of learning and performance in lead-exposed rodents (see Table 2). The most common task has been the maze. The use of mazes appeared very early in the history of behavioral assessment of rodents. They had a certain degree of face validity in that rats, which in their natural environment were noted for their complex tunnel systems, were required to make use of their natural predilection for running through confined areas. The evolution of maze configuration has been one of increasing simplification as highly complex, nonstandardized, multiple-choice-point mazes have been replaced by simple, standarized, single-choice-point T-mazes. Use of the single-choice-point tests on successive trials

Table 2
PROTOCOLS USED FOR THE STUDY OF ANIMAL LEARNING

Species	Behavioral task: Apparatus	Reward[a]	Task[a]	Lead exposure: Period[c]	Level[d]	Number (per test group): Litters	Subjects	Growth[e] rate	Blood lead μg/dl: Peak	At test	Learning performance	Ref.
Rat	Water T-maze	N	Si.BD	PG,G,L	270 GAV[f]	4	17	N	?	?	Impaired	12,40
	T-maze	P	Su.BD	L	100 W[g]	?	6	N	?	?	Impaired	35
	T-maze	P	Su.BD	L	25 GAV[f]	?	?	N	?	?	Impaired	
	T-maze	P	Su.BD	L (first 10 days)	35 GAV[f]	?	5—6	N	46	?	Impaired	
	T-maze	P	Su.BD	L (last 11 days)	35 GAV[f]	?	5—6	N	20	?	No effect	
	T-maze	P	Su.BD	L (last 11 days)	70 GAV[f]	?	5—6	N	19	?	No effect	
	T-maze	P	Su.BD	L (last 11 days)	140 GAV[f]	?	5—6	A	?	?	Impaired	
	T-maze	P	Su.BD	Birth to day 10	5 IP[f]	?	7	N	288	23	Impaired	
	Water T-maze	N	Sp.D	Various (8 days to 5 weeks)	100 IP[f]	?	66	?	?	?	No effect	52
	Shuttle box	N	2	5 weeks	100 IP[f]	?	8	?	?	?	No effect	
	Y-maze	P	Si.BD	PG,G,L,PW	2070 DT[g]	?	4	A	?	?	Impaired	45
	Shuttle box	N	2	PG,G,L,PW	2070 DT[g]	?	5	A	?	?	Improved	
	Shuttle box	N	2	PG,G,L,PW	207 DT[g]	?	12	N	?	?	Altered	
	Shuttle box	N	2	PG,G,L,PW	2070 DT[g]	?	12	A	?	?	No effect	
	Operant chamber	P	DRL-(20 sec.)	L	200 GAV[f]	—	6—7	A	?	?	Altered	70
	Shock grid	N	Flinch	L	109 546 W[g]	3	10	N	29,42	5,9	No effect	51
	Shock grid	N	SEA	L	109 546 W[g]	3	10	N	29,42	5,9	Less aggressive	
	Operant chamber	P	Su.BD	L	109 546 W[g]	3	10	N	29,42	5,9	No effect	

T-maze	P	Si.BD	Adult	2730 W	?	4—6	?	?	?	No effect	58
T-maze	P	Sp.D	Adult	2730W	?	4—6	?	?	?	Impaired	
E-maze	P	Sp.D	L	5,16,49 GAV[e]	?	?	N	33,174,226	15,23,56	No effect	39
E-maze	P	Ta.D	L	5,16,49 GAV[e]	?	?	N	33,174,226	?	Impaired on reversal	
E-maze	P	VD	L	5,16,49 GAV[e]	?	?	N	33,174,226	?	No effect	
2-Compartment chamber	N	I	L	5,16,49 GAV[e]	?	?	N	33,174,226	?	Impaired	
2-Compartment chamber	N	PA	L	5,16,49 GAV[e]	?	?	N	33,174,226	?	No effect	
Operant chamber	P	Te.D	L	5,16,49 GAV[e]	?	?	N	33,174,226	?	Impaired	
Operant chamber	P	FR	PG,G,L,PW	750W[f]	5	10	A	?	?	Impaired	64
			PG,G,L	750 W[f]	5	10	A	?	?	No effect	
			PW	750 W[f]	5	10	N	?	?	No effect	
CF-maze	P	Maze learning	Adult, PW	2.7,4.4, 6.6 IP[f]	?	8—10	A	?	?	No effect	18
CF-maze	P	Maze learning	L	4.4 IP[f]	17	36	A	?	?	Impaired	
Shuttle box	N	2	3—21 days postpartum	5,15,44 GAV[f]	6—7	28—34	?	11,21,23	?	Impaired	38
2-Compartment chamber	N	PA	3—21 days postpartum	5,15,44 GAV[f]	?	5—8	N	18,61,71	?	No effect	59
Shuttle box	N	1			?	5—8	N	18,61,71	?	No effect	
Shuttle box	N	2			?	5—8	N	18,61,71	?	Impaired	
Operant Chamber	N	Sp.D			?	5—8	N	18,61,71	?	Impaired reversal	
Operant Chamber	P	FI Schedule	PW(day 22—57)	50,300, 1000 W[e]	—	3	?	9,28,40	?	Altered	68

Table 2 (Continued)
PROTOCOLS USED FOR THE STUDY OF ANIMAL LEARNING

Species	Behavioral task: Apparatus	Reward	Task[a]	Lead exposure: Period[a]	Level[b]	Number: Litter per test group	Number: Subjects per test group	Growth[a] rate	Blood lead μg/dl: Peak	Blood lead μg/dl: At test	Learning performance	Ref.
Rat	Operant Chamber	P	VI 30 Schedule	PW(Day 90—126)	.09—52 IP[c]	—	?	?	?	?	Altered	67
	Lashley Jumping Stand	P	Si.FD & SD	PG,G,L,PW	745 DT[d]	—	10	N	29	29	Impaired	49
	Operant Chamber	P	FI Schedule	PG,G,L	750 W[e]	5	10	A	?	?	No effect	65
	Operant Chamber	P	FI Schedule	PG,G,L,PW	750 W[e]	5	10	A	?	?	Altered	
	Water T-maze	N	Si. BD & FD	PG,G,L	1000 W[e]	5	10	A	?	?	Impaired	41
Mouse	Water T-maze	N	Sp. D	Adult 1 Day	100 IP[c]	—	8—10	?	?	?	No effect	57
	Water Y-maze	N	Sp.D	Adult	5460 W[e]	—	10	?	?	?	Impaired	
Sheep	Operant Chamber	P	AD	Adult 9 weeks	100 GAV[f]	—	4	?	?	?	Impaired	16,44
	Operant Chamber	P	FI Schedule		1000 DT[d]	—	5	?	30	30	No effect	
	Operant Chamber	P	FI Schedule		530 DT[d]	—	5	?	17	17	No effect	
Sheep	CF—maze	P	Maze learning	G	2,3,4,5,/ DT	—	6—8	?	17—25	9—14	No effect	42,43

	CF—maze	P	Maze learning	5 days—12 weeks postpartum	2,4,8,16 DT[3]	—	4	?	57,81, 123,162
	Operant Chamber	P	Si. FD & SD	G	2,3,4,5, DT[3]	—	6—8	?	17,25
	Pigeon Operant Chamber	P	Multiple FR, FI	Adult	6.25 GAV[3]	—	2	?	9,14
					12.50 GAV[3]	—	5	?	285,412
					25.0 GAV[3]	—	6	?	285,311
	Operant Chamber	P	SPS	Adult	6.25 GAV[3]	—	4	N	398—848
								?	624—3415
	Monkey WGTA	P	—	L,PW	0.3,1.0	—	4	—	1360—2320
	WGTA	P	FD	L,PW	0.5 GAV[3]	—	4	N	35—70

	CF—maze	P	Maze learning	5 days—12 weeks postpartum	2,4,8,16 DT[3]	—	4	?	57,81, 123,162
	Operant Chamber	P	Si. FD & SD	G	2,3,4,5, DT[3]	—	6—8	?	17,25
	Pigeon Operant Chamber	P	Multiple FR, FI	Adult	6.25 GAV[3]	—	2	?	9,14
					12.50 GAV[3]	—	5	?	285,412
					25.0 GAV[3]	—	6	?	285,311
	Operant Chamber	P	SPS	Adult	6.25 GAV[3]	—	4	N	398—848
								?	624—3415
	Monkey WGTA	P	—	L,PW	0.3,1.0	—	4	—	1360—2320
	WGTA	P	FD	L,PW	0.5 GAV[3]	—	4	N	35—70
	Operant Chamber	P	SPS	Adult	6.25 GAV[3]	—	4	N	50,83
								—	50,83

and the behavior which is measured. The behavior which is generated depends on the functional status of the nervous system and the organism's interaction with the environment (most notably the test environment). The behavior which is measured depends on the test apparatus.

Tapp[28] compared seven different measurements of motor activity in the rat, including measurements in running wheels, photocell cages, Williamson (jiggle) cages, and lever-pressing activity. Their results argue that these different test procedures are measuring different components of behavior and that these components are independent in normal animals.

Experiments have also been reported which manipulate the status of the nervous system in very discrete ways resulting in behavioral changes which are apparatus-dependent. Capobianco and Hamilton[29] produced discrete lesions in various brain areas and measured activity with three different methods: open field, stabilimeter, and activity wheels. Lesions were placed in the fornix, diagonal band, and the medial forebrain bundle. All lesions produced an increase in locomotor activity when measured in the running wheel. On the other hand, activity in a stabilimeter either increased, decreased, or showed no change depending on the site of the lesion. Finally, measurements of both open-field ambulation and rearing appeared to be insensitive to these lesions. Any conclusion concerning the behavioral effects produced by lesions of the diagonal band, for example, would be either incorrect or incomplete if only one measure of activity were taken. Obviously an increase, decrease, or no change in activity has meaning only with regard to the particular test environment.

Similar environment-dependent behavioral responses are seen in the response of animals to drugs. Thus, Stewart[30] reported that administration of scopolamine (a cholinolytic agent) increased locomotor activity over control levels when animals were tested in a simple open field (3 ft × 3 ft). On the other hand, scopolamine-treated animals were less active than controls when the complexity of this environment was increased by inserting partitions which divided the field into either two or four compartments.

We see therefore, that activity is not a unitary measure of behavior. Not only do normal animals exhibit different behaviors in different test situations, but experimental manipulations which produce relatively well-defined changes in the functional status of the nervous system also produce behavioral deficits which are manifested differently in different test environments even when the behavioral endpoint is the same (i.e., ambulation). It is these types of changes (i.e., structural or biochemical/pharmacological) which will be produced by toxicant exposure. Therefore, the experimental difficulties become compounded when the toxicological insult is nonspecific in nature. Since lead-exposure has been shown to produce many nonspecific effects on the CNS (i.e., inhibition of energy metabolism, reduced transmitter release, etc.) it is not surprising that its effects on motor activity may vary with the experimental conditions.

4. Techniques for Quantifying Activity

There are several common methods of measuring locomotor activity in animals: (1) photocell cages, (2) running wheels, (3) stabilimeters and jiggle cages, (4) tilt cages, (5) open fields, (6) proximity counters, and (7) direct observation. All have been used to assess the activity of lead-exposed rodents.

For the most part, the open-field and photocell cages have been used to assess the animal's short-term responses to novel environments. The testing period lasts from a few minutes in the case of open-field measures to several hours with automated photocell cages. In both cases, however, the experimenters are attempting to use locomotor behavior as an index of the inferred processes of reactivity, exploration, and habituation. Thus data collection is focused on changes in the rate of behavior (locomotion,

rearing, etc.) during the test interval. In contrast to this, a few investigators have chosen to examine the rate of behavior exhibited under stable environmental conditions. Running wheels and residential mazes in which the animal resides for a period of several days to several months have been used to study circadian rhythms and long-term activity profiles.

5. Factors Influencing Activity Assessment

Numerous internal and external factors can influence activity levels thereby causing individual differences in activity. Since this individual variability can be quite large (large enough to completely obscure any treatment-related effect), it is important that these factors be identified and controlled. The principal internal factors are (1) species and strain, (2) age, (3) sex, (4) endogenous rhythms, (5) nutritional state, and (6) previous experience. Few of these factors have been explored in any systematic manner in regard to their interaction with lead exposure. This no doubt contributes to the poor level of agreement across laboratories engaged in lead research. Finally, several external factors can affect spontaneous motor activity. These include (1) extraneous noise, (2) temperature and humidity, (3) illumination level within the test environment, and (4) test and housing conditions (i.e., reared alone, tested alone or group-housed and group-tested). It may appear, however, that the extreme liability of general activity limits its utility as a dependent variable of interest in lead research. There can be no doubt that a lack of awareness and/or inattention to necessary control procedures has resulted in many uninterpretable and irreproducible results. However, to the extent that experimenters attend to a few simple precautions, variability can be controlled and will yield a powerful tool for assessing the neurophysiological state of the animal. The interested reader is referred to several reviews on locomotor activity and factors which influence these measurements.[31-34]

D. Review of Animal Learning Studies

The following section provides a review of individual published reports and dissertation research reporting the effects of lead exposure on the performance of test animals in learning tasks. Two tables are included in an attempt to structure the learning/performance literature and facilitate evaluation. Table 3 provides an overview of the pertinent studies including exposure conditions, testing conditions, and results. Table 3 separates the data along two dimensions: (1) tasks which reportedly are or are not sensitive to changes arising from the exposure conditions, and (2) the stage of learning/performance during which effects are or are not demonstrable. The acquisition column includes investigations of the rate at which animals form associations between stimulus and reinforcement conditions. Measures utilized to quantify the process are number of days, trials, or problem presentations required to reach some predetermined level of performance. The percentage of the test population attaining the defined criterion per unit time is also a common measure. The performance column includes studies of the quantitative nature of the behavior after the desired criterion has been attained. The reversal/extinction column contains studies of behavior observed following the removal of reinforcement (extinction) and alteration of the stimulus conditions which signal reinforcement (reversal).

1. Effects of Lead on Discrimination Learning

a. Brown[35]

Brown's work[35] was one of the first studies in this area and currently provides the only available data which permits a direct comparison of the roles of route, level, and timing of lead exposure on the resultant blood-lead profile and behavioral development. The behavioral task employed by Brown was a successive brightness discrimi-

Table 3
STAGE OF LEARNING

Acquisition	Performance	Reversal Extinction
Treatment Effects Present		
Brady et al.[40] ▪	Barthalmus et al.[19] ▲	Bushnell et al.[61] ▲
Brown [15] ▲	Ogilvie [57] ▪	Overmann [60] ▪ ▲
Carson et al. [43] ▲		Sobotka et al. [58] ▪
Driscoll & Stegner [45] ▪ ▲	Padich & Zenick [64] ▲	Rice & Willes [62] ▪
Hastings et al. [50] ▲	Shapiro et al.[67] ▲	
Lanthorn & Isaacson [38] ▲		
Overmann [60] ▪	Slechta [47] ▲	
Snowdon [186]	Zenick et al.[65] ▲	
Sobotka et al.[58] ▪		
Winneke et al.[49] ▲		
Zenick et al.[41] ▪		
Treatment Effects Absent		
Brown et al.[52] ▪		
Carson et al.[43] ▲		Overmann[60] ▪
		Sobotka et al [58] ▪
Hastings et al.[50] ▲		
Overmann[39] ▪ ▲		
Sobotka et al.[58] ▪		
Winneke et al.[49] ▲		

▪ Negative reinforcer.
▲ Positive reinforcer.

nation conducted in a T-maze. The reinforcer was a 30-sec access to water. Although the task is described as a brightness discrimination, Brown[16] has since indicated that the discrimination was essentially a light on-light off discrimination. A task of this type is relatively difficult, since the animal is not able to compare the two stimulus conditions simultaneously, as is the case in a simultaneous discrimination task. In a successive discrimination one of two possible stimuli is presented during each successive trial. The subject must compare the immediate simulus with his memory of the two stimulus conditions in order to arrive at a decision to turn right or left. Impairment of performance on this type of task is often reported in adult hippocampectomized animals. Brown's observation of deficits on this task is in part responsible for the selection of other "hippocampal-sensitive" tasks by investigators in their behavioral examination of lead-exposed animals, e.g., spontaneous alternation,[37] reversal learning,[38] and extinction.[39] However, such a rationale may not be warranted, since in most hippocampal lesion studies both the lesion and the behavioral measurement are made in the adult. The pattern of behavioral changes seen in adult animals following neonatal insult, as is the case in many lead studies, may be quite different.

Brown[15] exposed suckling rats to lead via the milk of lead-treated dams as well as by direct intraperitoneal (i.p.) injection of the pups. Lead was administered daily to three age groups: group 1 from days 1 to 10; group 2 from days 11 to 20; and group 3 from days 1 to 20. No information is reported which would indicate that pups suckling lead-exposed dams from days 1 to 10 were cross-fostered. Therefore, lead exposure may have continued beyond day 10 due to a residual lead contamination of maternal milk. Only limited data are provided pertaining to growth rate during the exposure period. There were no differences in the body weights of various treatment groups at

the time of testing. Blood-lead concentrations covered a large range as a function of the exposure protocol (from 20 ± 2 μg/dℓ to 288 ± 34 μg/dℓ). There was no apparent correlation between the blood-lead concentration during development and subsequent behavioral impairment; e.g., pups injected with 5 mg/kg lead from day 11 to 21 had blood-lead levels of 198 ± 17 μg/dℓ (day 21) and exhibited no behavioral impairment, while pups exposed to lead via dam's milk during days 1 to 10 had blood-lead levels of 46 μg/dℓ (day 11) and exhibited a 55% decrease in performance. Brown suggests these data indicate that age at exposure is the critical factor and not the absolute level of lead in the blood.

However, the behavioral deficits in pups exposed via maternal milk may be due to alterations in the quality of the maternal milk[10] and may be unrelated to the relatively low level of lead (46 μg/dℓ) found in the blood. Consistent with this hypothesis are the data presented by Brown. The data show that direct i.p. injection of the pups from days 1 to 10 produced blood-lead levels of 288 μg/dℓ (day 11) and yet behavioral impairment was of the same order of magnitude (45% of control scores) as that seen following lead exposure via maternal milk from days 1 to 10 (46 μg/dℓ; 48% of control score). It could be that the T-maze test employed by Brown was insensitive to dose-response effects of lead or that lead-induced alterations in maternal milk (e.g., altered trace metal content) may render the neonates more sensitive to the lower blood-lead concentrations obtained in maternal milk.

A more complete evaluation of the data reported by Brown[35] is difficult, since data are not reported for each exposure protocol that was evidently run. Furthermore, the behavioral data are often reported as "percent of control", which hinders evaluation. In those few instances where group means and variance are reported, there is a disturbing degree of variability between the learning scores obtained by control rats derived from three independent groups (8.0 ± 0.7; 4.2 ± 0.8; 6.4 ± 1.0). This variability equals the magnitude of change seen between control and lead-exposed groups within any experimental run. This may be a reflection of the sensitivity of the test to environmental conditions at the time of testing, which is a common problem with maze tasks, or it may be due to behavioral genetic variance present in the random-bred stock used in the study.

b. Brady et al.[40]

Brady et al.[40] explored the influence of parental lead exposure on subsequent learning ability of the rodent offspring. One or both of the parents were exposed to lead acetate, 500 mg/kg, for 60 days prior to mating. At that time, the rats were mated to yield four treatment groups: group Pb-Pb, both parents received lead; group Pb-N, only the dam was exposed to lead; group N-Pb, only the male received lead; and group N-N, neither parent exposed to lead. Dams were continued on their assigned treatment throughout gestation and lactation.

Testing of both male and female offspring began at 30 days of age. The task required a black-white discrimination in a water escape T-maze. Two days of pretraining preceded the 4 days of acquisition during which the rats were run five trials per day. Number of errors and escape latencies were recorded. The three lead exposure groups exhibited 48 to 91% longer escape latencies during pretraining and 36 to 67% longer escape latencies during acquisition than did controls. In addition, all three lead exposure groups committed twice as many errors as did the controls during acquisition. Zenick[66] was able to replicate the error data previously reported by Brady et al.[40] However, he was unable to replicate the previously observed latency effects during pretraining.

The error data obtained by Brady et al.[40] during acquisition is not necessarily indicative of a lead-induced learning deficit, since large differences in escape latencies were demonstrated during the pretraining sessions. Thus initial performance differences may have been responsible for the apparent learning deficit. It is quite surpising to see the same type and level of behavioral disruption irrespective of parental exposure conditions. Although no blood- or tissue-lead concentrations were obtained, it is obvious that the deficits seen in the paternal exposure group (group N-Pb) cannot be accounted for on the basis of an elevated lead body-burden in the offspring. Since the subjects within a treatment group all derived from only three litters, it is possible that a sampling error resulted in the chance assignment of genetically different animals to the control group. Such an occurrence was made possible by the use of genetically randombred rats. An alternate explanation might involve a selective gametotoxic effect of lead on either the sperm or egg. If only selected sperm from the entire gametic population were affected by the presence of lead, i.e., removed from the gene pool, then the result could be a shift in the distribution of observed behavioral responses in the resultant offspring. It is not possible to resolve such issues unless large numbers of litters are represented in the treatment group or a more genetically uniform animal population is used.

c. Zenick et al.[41]

Zenick et al.[41] have replicated certain aspects of the Brady et al.[40] study. In this study, dams were exposed to 1000 mg lead acetate per kg of body weight for 70 days prior to mating. This treatment was continued throughout gestation and lactation, at which point exposure was terminated. Testing began at 30 days of age with animals receiving 10 trials per day for 10 days on a brightness discrimination task conducted in a water-escape T-maze. This task was followed by a shape discrimination problem in the same apparatus. Analysis of results revealed that the lead-exposed pups made significantly more errors than the controls but had significantly shorter swimming times on both the brightness- and shape-discrimination tasks. Zenick et al.[41] interpreted these effects as being due to a failure to attend to relevant discriminative cues. Thus the poor learning may have been due to an underlying attentional deficit. A more direct examination of attentional processes, e.g., as obtained in a vigilence task, is warranted.

d. Carson[42,43]

Carson[42] and Carson et al.[43] conducted a series of studies of visual and auditory discrimination learning in sheep subjected to moderately elevated blood-lead levels during prenatal and/or postnatal development. Two groups of ewes, 10 ewes per group, were fed elemental lead sufficient to maintain blood-lead levels of about 18 $\mu g/dl$ thoughout gestation, while controls had blood-lead levels of about 5 $\mu g/dl$. Lambs from the control, low-, and high-lead groups, had blood-lead levels of 6, 17, and 25 $\mu g/dl$, respectively, at 2 to 4 weeks of age, and 4, 9, and 16 $\mu g/dl$, respectively, at 10 to 12 weeks of age when they were weaned. From 10 days to 3 months of age, the lambs were tested on a series of 16 closed-field maze problems. No significant differences between treatment groups were observed. At 5 months of age the lambs were trained on a simultaneous two-choice, non-spatial visual discrimination task employing six different pairs of stimuli. They were run to a criterion of 28 correct responses in a 40-trial session for 3 consecutive days. A significant decrement in performance was found for the high-exposure group. This significant effect was essentially due to one problem in which four of the six high-exposure lambs failed to learn a size discrimination within the 35-day maximum testing period. Problem 6 differed from the preceding five problems in that it required a size discrimination rather than a form discrimination. The task difficulty could have arisen from (1) the type of discrimination

required; i.e., size, (2) the change from form to size discrimination, or (3) the overall high level of difficulty of this particular problem.

At 10 to 13 months of age, the lambs were retested on the original six problems plus two new size discrimination problems.[42] The new problems were similar to Problem 6 in that they required a size discrimination. Upon re-test no treatment differences were found in the performance of the lambs on any of the size discrimination problems. Significant group differences were only observed on Problem 5, a right-left mirror image discrimination. The lead-exposed lambs initially had difficulty with this problem at 5 months of age; however, at that time the group differences were not statistically significant. These results lead Carson[42] to reinterpret his data. In the initial report the lambs had been tested only at 5 months of age. At that time it was suggested that lead had a specific effect on size discrimination (Problem 6) but not form discrimination (Problems 1 to 5). After acquiring additional data at 10 months of age Carson suggested that the difficulty arises in mastering new behavioral tasks; that is, the size discrimination problem represented a different type of task than the earlier form discrimination problems. Having once been exposed to the new type of problem at 5 months, the lambs had no further difficulty with size discriminations when tested at 10 months of age. If such an interpretation is correct, then one would expect lead exposure to adversely affect "reversal" and extinction processes as has been reported by several investigators.[38,39] A second implication of Carson's work is that repeated testing of animals may result in the disappearance of behavioral differences as the animals gain increasing familiarity with the problem.

At 15 months of age these same lambs were trained on an operant auditory discrimination task. In all, the lambs were tested on seven different auditory discrimination problems (200 Hz vs. 5000 Hz, easiest problem; 620 Hz vs. 1200 Hz, most difficult problem).

A significant treatment effect demonstrated that the high-lead exposure group required more days to acquire the first and easiest discrimination than was required by the low-lead or control groups. Again these data suggest difficulty with learning the new task of auditory discrimination and not difficulty with a particular class of discrimination.

Carson[42] and Van Gelder et. al.[44] also explored the influence of postnatal lead exposure (day 5 through day 84) on the previously described auditory and visual tasks. Although the exposure regimen resulted in blood leads in excess of 150 $\mu g/dl$ during exposure, no significant treatment effects were observed. These data support Brown's contention[35] that the critical period for lead toxicity occurs early in life; i.e., postnatal exposure for the rat and *in utero* exposure for the precocial lamb.

e. Driscoll and Stengner[45]

Driscoll and Stengner[45] also examined the effects of lead exposure on discrimination learning. Rats were continuously exposed to 2,000 ppm of lead prior to mating and throughout gestation and lactation. Offspring were then continued on the same treatment regimen. In the first experiment animals were required to discriminate between a lighted and an unlighted alley in a Y-maze. Animals were run 30 trials per day to a criterion of 90% correct on 2 consecutive days. Following initial acquisition, the rats were subjected to five consecutive reversals on the same problem. Lead-exposed offspring (N = 4) made significantly more errors (90% increase) during the initial acquisition of the simultaneous visual discrimination than did control rats (N = 4). More errors were also made during the first reversal (29% increase); however, this difference failed to achieve statistical significance given the small number of subjects used. No differences were seen on subsequent reversals. These data support Carson's[42] contention that lead exposure impairs an animal's ability to deal with new problems.

Driscoll and Stengner[45] also examined the learning process in a two-way shuttle-box avoidance paradigm. Two exposure levels, 2000 and 200 ppm, were used. In each group twelve animals were tested. No indication was given pertaining to assignment of animals from litters to treatment groups. Therefore, the role litter effects may have played cannot be assessed. No significant differences were seen in the rate of avoidance acquisition for the control and high-lead exposure groups. However, significant impairment in rate of acquisition was seen in the low-exposure group relative to the high-exposure group. This reverse dose-response curve, i.e., larger effects at lowest doses, has also been reported by Slechta[47] and Rafales et al.[48] It is possible that the dose-response function may not be monotonic.

f. Winneke et al.[49]

Winneke et al.[49] have also recently examined visual discrimination learning in rats exposed to lead *in utero* via dam's milk, and postweaning via drinking water (0.14% lead acetate). Ten dams were used in each treatment group. This protocol produced blood leads of about 27 $\mu g/d\ell$ at day 16 and 29 $\mu g/d\ell$ in 190-day-old lead-exposed offspring. The task was a Lashley jumping stand with either one of two problems: "easy", vertical vs. horizontal stripes, and "difficult", large circle. The rationale for the exposure protocol and behavioral test was an attempt to confirm the findings of Carson et al.[43] using a different species. Using the jumping stand, ten control and ten lead-exposed rats were trained to a criterion of 13 out of 15 correct responses on 2 consecutive days.

Winneke et al.[49] found no effect on the acquisition of the "easy" discrimination. However, on the "difficult" discrimination, eight out of ten controls reached criterion within 27 days whereas only one of the lead-exposed animals did so. It is unclear whether the same rats were tested on both problems. Winneke et al.[49] also report that epidurally recorded flash-evoked responses indicate that lead does indeed interfere with visual function. No data were presented to support this statement. The findings of Winneke et al.[49] appear to support the earlier findings of Carson et al.[42] of behavioral changes at internal lead exposure levels of less than 40 $\mu g/d\ell$.

g. Hastings et al.[50]

Hastings et al.[50] reported a failure to find any lead effects during either the acquisition or reversal of a successive brightness discrimination conduted in a two-bar operant chamber. This was surprising since the low-dose exposure group was similar to that of Brown,[35] i.e., 0.02% lead acetate (109 ppm of lead) in the drinking water of a lactating rat. It may be that an aspect of spatial behavior for T-maze performance is not necessary for performance in the operant chamber.

In order to more fully explore the issue, a second series of studies conducted by Hastings et al.[51] examined the performance of lead-exposed offspring in three different learning tasks employing different types of discrimination and different types of testing equipment. The dams received either 0, 109, or 1090 ppm of lead in their drinking water during the lactation period. No effects on growth rate were observed.

In the first study, these rats were tested on a simultaneous (bright-dim) visual discrimination task. This task was very similar to the previously mentioned successive visual discrimination task[50] with one important difference: whereas previously the rats had to press one of two bars depending on whether a single light came on bright or dim, in the simultaneous discrimination the correct bar was also signaled by the onset of a cue light located directly above the bar. This was an easier task for the rat to acquire and reduced the lengthy acquisition phase found in the successive visual discrimination task. It took the control group 25 days to acquire the original task. How-

ever, almost 40% of the lead-exposed animals failed to acquire the discrimination before the testing was terminated at 50 days. A Kruskal-Wallis analysis of variance on number of days to reach criteria (45 out of 50 correct responses on 3 consecutive days) showed that the lead-exposed rats performed more poorly than controls in acquiring the task ($p < 0.05$). Since many of the rats did not acquire the task, it was impossible to run a reversal procedure.

The rats were next tested on a successive visual discrimination task, but were run in a T-maze instead of an operant chamber. In this experiment the rat had to learn to turn right in the T-maze for reinforcement if a bright light was on and left if the light was dim; i.e., the same paradigm as was used by Brown.[35] Although the high-lead group took slightly longer to learn the task, the difference was not significant. The overall coefficient of correlation between performance on the simultaneous (operant chamber) and successive (T-maze) visual discrimination tasks was 0.04.

In the final task, the rats were again tested in the operant chambers on a discriminated go-no go paradigm. In this task, whenever the houselight came on, the rat could obtain reinforcement by performing a Fixed Ratio (FR) 20 response. A Kruskal-Wallis analysis of variance on days to criteria revealed no significant differences among the groups on either the original or reversal problem.

h. Brown et al.[52]

Several investigators have looked for behavioral changes after exposure of adult animals to lead or lead compounds, in some cases at doses which produce gross toxicity. For example, Brown et al.[52] found that neonatal and weanling rats given inorganic lead acetate (i.p.) showed no deficits in learning or memory in a water-escape maze at levels of exposure that were toxic. In the first experiment, 15 rats aged 5 weeks were trained for 15 trials in a T-maze and the next day tested for memory. Learning and memory were defined as five consecutive correct responses. The animals were then injected with lead acetate 100 mg/kg; i.p., on the first, second, and third days following the memory test. On the fourth day they were trained to reverse their position habit, i.e., to escape to the opposite arm of the maze. Memory was tested on the following day. During the experiment five of the animals died.

In the second experiment, ten 5-week-old animals received lead acetate for 3 consecutive days. Following the last injection, they were trained to escape to one of the arms of the water maze. Memory was tested the following day. During the experiment two animals died. A similar set of experiments was carried out on 8- and 21-day-old pups.

The authors found no significant effects of lead acetate on learning and memory in spite of the fact that all animals displayed marked locomotor impairment after the last injection and that some animals died in each group. Brown et al.[52] conclude that whereas lead acetate produces irreversible encephalitic damage in humans, it does not affect learning or memory in rats.

The experimental data presented do not permit such a sweeping generalization. First, the learning task was quite simple, perhaps too simple to discriminate between treated and control rats. Second, since no blood-lead determinations were performed we do not know if equal blood-lead levels were attained in all treated animals. The i.p. administration of lead salts is an undesirable procedure. Jugo and Kello[53] have reported that lead acetate in high doses forms complexes which are poorly and perhaps erratically absorbed into the bloodstream. Furthermore the injections often result in an extreme abdominal tenderness and in some cases, peritonitis. Thus, in the Brown et al. study[52] it is possible that lead absorption was highly variable resulting in death in some animals and no effect in others. Finally the high dosage resulted in death in some animals, perhaps those most sensitive to lead and most likely to have shown behavioral deficits had they lived.

i. Snowdon[18]

Snowdon[18] examined the effects of lead exposure at each of four developmental time periods: prenatally, during nursing, post weaning, and adulthood. Lead was administered i.p. The objections with this route of exposure have already been noted (see also References 35 and 52). The animals were randomly assigned to one of four injection groups: distilled water, or 5, 8, or 12 mg of lead acetate per kg of body weight. Injections were begun i.p. on the day of entry into the laboratory and were continued for 21 days, at which point testing was started. They were also continued through the subsequent 16 days of testing, for a total of 37 days of injections. In the weanlings, injections were begun at 22 days of age, with testing beginning on the 43rd day. The adults were approximately 100 days of age. Each group contained 14 animals, 7 males and 7 females.

The animals were tested in a modified Hebb-Williams maze. (The Hebb-Williams maze series represents a rather sophisticated series of problems which have been used to characterize the behavioral consequences of various brain lesions in rats.) Trained observers scored the animals' errors and recorded total errors and running time to the nearest second after each trial. The animals were presented with 4 practice problems, 1 each day, and then each of 12 test problems, 1 each day. Animals were tested until they reached a criterion of 4 out of 5 errorless trials or until they ran 48 trials, whichever came first.

The animals which received the highest doses of lead acetate, (12 mg/kg/day) showed signs of lead poisoning. Only 8 out of 14 adults and 10 of 14 weanlings survived to complete the entire test series. The animals which died were excluded from the analysis of the learning data.

Despite the successful production of symptoms with high doses and the use of a sensitive learning situation — the closed-field maze series — there were no significant differences in learning. The only measure to reach significance was an increased urinary ALA (d-aminolevulinic acid) level with lead injections.

None of the 17 pregnant females which were injected with 0.8 mg of lead acetate per 100 g/day delivered any offspring. In contrast, 12 of the 16 pregnant females injected with distilled water delivered with a mean litter of 8.6 pups. The lead-injected females demonstrated no overt signs of poisoning. They did not show the typical large weight gain of pregnancy, but they did gain a mean of 12 g over the course of the injections, a weight gain consistent with that of nonpregnant females over a similar period. Thus a dose of lead that failed to produce any symptoms in adult and weanling rats and that had no obvious effect on the inseminated females was sufficient to induce a 100% abortion rate.

The lead injections appeared to produce no symptoms in the nursing mothers. However, all pups of lead-injected mothers showed signs of developmental retardation. They were consistently 1 to 2 days slower in the time of eye opening, and their mean body weight at weaning was 64.5% that of the water-injected offspring. The analyses of the behavioral results indicated that rats whose mothers were injected with lead acetate during nursing made significantly more errors than did offspring of water-injected mothers. While lead-exposed animals did take more trials to reach criterion, this difference barely missed reaching significance (mean = 260.2 trials — lead exposed, 235.7 trials — controls). Comparison of running times per trial indicated that there were no differences between the animals. Thus the increased number of errors made by offspring of lead-injected mothers was not due to a motor deficit or a reduced level of motivation for food reward which might have been induced by lead exposure.

The investigator should be commended for his attempt to address the issues of dose-response and critical periods as well as for his use of biochemical correlates of lead toxicity and a relatively sophisticated behavioral test. Unfortunately the route and level

of exposure, as already discussed, leaves much to be desired. Furthermore, no data or discussion were provided which would permit an assessment of animal learning on individual problems within the maze series. Finally, no within-animal correlations were provided between urinary ALA and test acquisition. The latter might have shed some light on the issue of individual variation in sensitivity to lead exposure.

j. Ogilvie[55]

Ogilvie[55] treated 20 adult male CF-1 mice for 2 weeks with either a 1% lead acetate or sodium acetate drinking solution. The mice were then tested in a double-Y water maze. Swimming time, number of errors per trial, and trials to criterion were recorded for each mouse. Mice failing to reach the escape ladder within 60 sec were removed from the maze. Animals received a 1-min rest between trials. An animal reached criterion performance when it made seven consecutive escapes without an error. If a mouse failed to reach criterion within 21 trials, testing was terminated. No documentation of the amount of lead consumed or internal lead exposure, i.e., blood-lead levels, were provided.

Treated mice exhibited a depressed weight gain during the exposure period and swam the maze significantly more slowly than controls. This effect was not present on the first trial but became evident on subsequent trials, even when the error rate of the two groups was equal. Ogilvie[55] suggested that this effect might be attributed to lead-induced neuromuscular impairment. However the reduced food and fluid consumption of mice exposed to this level of lead (Morrison et al.[56]) and the resultant inanition is the more likely candidate when searching for the cause of this effect. Nine of ten controls and six of ten treated mice successfully reached criterion. No differences were seen in the number of trials to reach criterion, 11.6 ± 0.6 vs. 12.8 ± 0.5 for control and lead-exposed mice, respectively. However, lead-exposed mice did make significantly more errors enroute to attaining criterion performance, 5.3 vs. 9.5. The presence of an obvious performance deficit in the lead-exposed mice makes interpretation of this proported learning deficit less than straightforward. The fatigue the lead-exposed mice experienced in increasing degrees as trials progressed could have resulted in a greater level of stress. This in turn could interfere with the ability of these mice to attend to the salient cues necessary for learning to occur. More recently, Ogilvie,[57] using adult mice in a water T-maze, failed to find any impairment in the ability to retrieve information which was stored prior to a single intraperitoneal injection of 100 mg/kg of lead acetate. The problems inherent in this route of administration have already been discussed.

k. Lanthorn and Isaacson[58]

Lanthorn and Isaacson[58] like Brown,[35] postulated that aberrant hippocampal functioning might underlie some of the behavioral consequences of lead poisoning. Unlike Brown, however, they chose to explore this issue using adult rats. For 2 weeks prior to behavioral testing, ten adult male Long-Evans rats were exposed to 0.5% lead acetate in their drinking water. Then six experimental and four control rats were tested on the acquisition and reversal of a light discrimination to a criterion of nine out of ten correct responses on 2 consecutive days. Immediately following completion of this task, the animals were tested for their ability to acquire a spatial discrimination. Again the criteria was nine out of ten correct responses on 2 consecutive days. The investigators found no treatment-related effects during the light discrimination task. However, on the first day of testing on the spatial discrimination task, rats receiving lead took significantly more trials to reach criterion. This effect could be interpreted as an inability of lead-exposed rats to master new problems requiring different response strategies. This is reminiscent of the findings of Carson[42,43] reviewed in an earlier section.

Like Carson,[42] Lanthorn and Isaacson failed to detect any further treatment effects during continued testing on the spatial discrimination task. The limited number of subjects as well as the absence of any documentation of internal body burden of lead severely limits the utility of the data other than to provide limited support for Carson's hypothesis.

2. Performance of Lead-Exposed Rats on a Battery of Behavioral Tasks

Sobotka et al.[59] and Overmann[39] recently examined the effects of neonatal lead exposure on subsequent behavioral performance involving a battery of tasks. Their investigations utilized very similar exposure protocols.

a. Sobotka et al[59]

Sobotka et al.[59] intubated neonatal rats daily with 9, 27, or 81 mg of lead acetate per kg of body weight throughout the 3-week postnatal period of development. This resulted in blood-lead concentrations ranging from 18 to 71 $\mu g/d\ell$. The work of these investigators is of particular interest because they are one of the few groups attempting to examine not only behavioral effects, but also neurochemical, hematopoietic, and renal effects. They found behavioral changes in both weanlings and adult rats in a shuttle-box avoidance task (failure to escape shock by moving to the safe compartment) and in a habit-reversal task (failure to transfer responses to the alternate bar following the acquisition of a position habit in a bar-press avoidance task). No deficits were observed in exploratory or general motor activity, passive avoidance, or one-way avoidance. Three separate groups of animals were used to replicate these findings and biochemical effects were also reported. These effects included (1) unaltered monoamine metabolism, adrenal steroid levels, or thyroidal thyroxine levels, (2) depressed cholinesterase activity in the telencephalon only, (3) inhibition of blood and brain ALAD (ó-amino-levulinic acid dehydratase) activity, and (4) an increase in kidney weight.

Statistically significant changes in kidney weights were seen in all three replications at the lowest exposure level (blood lead = 18 $\mu g/d\ell$. Decreases in hematocrit, hemoglobin level, shuttle-box performance, and habit reversal were seen at blood-lead levels equal to or in excess of 61 $\mu g/d\ell$. Statistically significant changes in blood and brain ALAD activity were only seen at the highest exposure level, perhaps because of the low number of subjects sampled. Thus, in these studies the sensitivity of the behavioral system to lead appeared to equal that of the hematopoietic system. Unfortunately, the exposure protocol did not produce blood-lead levels in the critical range between 18 and 61 $\mu g/d\ell$.

Sobotka et al.[59] addressed another difficult problem in this study, i.e., within-laboratory replication of results. Most of the dependent measures were obtained on three separate replication attempts. Difficulties in replication are quite evident from the data presented. Furthermore, the difficulty was seen irrespective of the system studied or the methods employed. For example, the same magnitude of hematological, neurochemical, or behavioral effects was not always present at the same lead-dosage levels obtained on successive replications. Other investigators have reported similar difficulties in obtaining within-laboratory replication of results. This problem might be attributable to a high degree of individual animal variability in response to lead exposure since such poor reliability is not ordinarily encountered with the parameters in question.

b. Overmann[39,60]

Overmann [39,60] used a similar exposure regimen to examine the influence of lead on a battery of eight behavioral tasks, as well as hematocrit and organ weight. Like So-

botka et al.,[59] Overmann found that daily intubation of 0, 10, 30, or 90 mg/kg of lead acetate produced decreased hematocrit and increased adrenal and kidney weights. These effects were observed at the two highest doses. The organ weight effects were still present at 133 days of age. The three levels of lead exposure had no effect on growth. However, neonatal lead exposure produced behavioral effects including impairment of motor coordination (rotarod test), response inhibition ability (operant delayed response), and reversal learning of a tactually-cued conditional discrimination. The lead treatment had no effect on simple learning (turning response in E-maze), complex visually-cued learning (conditional discrimination in E-maze), and visual acuity (optokinetic test). Acquisition and extinction of passive shock avoidance were not affected by lead exposure, but both acquisition and extinction of active avoidance were affected.

In comparing the Overmann[39] and Sobotka et al.[59] studies, one finds considerable differences in the blood-lead levels which resulted from essentially identical exposure protocols (see Table 2), but the basis for these differences are not apparent at this time. Two areas of disagreement exist between the studies: (1) with respect to locomotor activity levels (see further discussion of this finding in the section on locomotor activity below), and (2) with respect to one-way avoidance. Overmann,[39] like Hastings et al.,[50] found a decrement in both the acquisition and extinction of a one-way avoidance response. The failure of Sobotka to observe such an effect may have been a result of the manner in which the foot-shock was delivered. The shock terminated automatically after 5 sec if the rat had not already avoided or escaped. Such a procedure often induces a "freezing" response and subsequent failure to acquire the desired response. Since a similar procedure was also used by Sobotka and Cook[38] in a two-way avoidance task, where they noted a high incidence of "freezing" behavior, it may be that these shock-induced learning paradigms are actually measuring differences in reactivity of lead-exposed animals to shock or other stimuli and not differences in cognitive ability.

3. Effects of Lead on Visual Acuity

a. Bushnell et al.[61]

While numerous investigators have reported deficits in tasks requiring visual discrimination, only one report by Bushnell et al.[61] has specifically attempted to assess the visual acuity of the lead-exposed animal. These investigators used infant rhesus monkeys, a Wisconsin General Test Apparatus (WGTA), and Landolt ring stimuli to assess acuity under four different light intensity conditions. The monkeys were exposed daily, beginning on day 5 and continuing to day 365, to an oral lead intake adjusted to produce blood leads of 55 μg/dℓ in the low-lead group (N = 3), and 85 μg/dℓ in the high-lead group (N = 3). Unfortunately, the blood leads of the three high-lead monkeys reached 300, 137, and 152 μg/dℓ during the fifth, sixth, and ninth week, respectively. Four control monkeys were also tested.

Significant decrements in visual acuity were seen in the high-lead group. Severity of the performance decrement was a function of the difficulty of the discrimination and the ambient lighting level. The deficits were attributed to a deficit in scotopic function. It was not possible to attribute the deficit to the blood-lead level at time of testing, i.e., 85 μg/dℓ, because of the earlier transient high lead levels of approximately 200 μg/dℓ.

b. Rice and Willes[62]

Eight monkeys, four controls and four treated from day 1 of life with 0.5 mg of lead acetate per kg of body weight per day, were studied. The monkeys were from 421 to 714 days old at the start of testing. Blood-lead levels peaked between 35 and 70 μg/

dℓ at about 200 days of age, dropped to 20 to 50 μg/dℓ by 400 days of age and then stablized at this level for the remainder of the test period. Control blood-lead levels were stable and below 5 μg/dℓ. These lead levels are slightly lower than those reported by Bushnell et al.,[61] and apparently the present authors did not encounter any problems such as the "overshoot" reported by Bushnell et. al.[61]

The task was a form discrimination (cube vs. triangle) carried out in a WGTA. Monkeys were tested ten trials a day. The position of the correct stimulus was determined by a Gellerman series with a "between-trial" correction procedure. Criterion for learning the discrimination was 90% correct in a ten-trial daily session. Following original acquisition, the monkeys were run through 20 consecutive reversals, i.e., the correct stimulus was reversed from cube to triangle or vice versa.

The lead-exposed animals learned the original form discrimination more rapidly than did the controls. However, during repeated reversals, there was a general tendency for the control group to learn the reversals more quickly than the treated animals. Bushnell[63] reported a similar retarded reversal learning curve as compared to controls in a similar two-choice discrimination reversal paridigm using monkeys.

4. Effects of Lead on Schedule-Controlled Behavior

a. Padich and Zenick[64]

Padich and Zenick[64] examined the effects of neonatal vs. adult lead exposure on fixed-ratio performance. Twenty-one day-old female rats were exposed to daily doses of 750 mg/kg of lead acetate via a restricted water intake regimen for 70 to 80 days prior to mating. Treatment was then continued throughout gestation and nursing, during which time offspring were indirectly exposed via the dam. At weaning, litters from half of the treated and control mothers were placed on direct lead exposure for the remainder of the experiment. This manipulation yielded four groups for testing: group Pb/Pb, developmental and postweaning exposure; group Pb/C, developmental exposure only; group C/Pb, postweaning exposure; and group C/C, no exposure to lead acetate treatment. Beginning at 42 to 49 days of age, offspring were trained to bar press on an FR 20 schedule of reinforcement and then received 20 sessions each 20 min in length. Analyses revealed that group Pb/Pb received significantly fewer reinforcements per minute across sessions than the other three groups, and also took significantly longer to emit each 20-response block. Contrary to the majority of previous reports in the literature, these data suggest that rats may not be impervious to postweaning lead exposure, particularly when there is a history of lead exposure during development.

b. Shapiro et al.[67]

Shapiro et al.[67] examined the influence of adult lead exposure on the performance of rats in a light-cued go-no go operant discrimination. For water reinforcement, fourteen male albino rats were trained to press a lever. During a 10-min "light on" interval, rats received reinforcement on a 30-sec variable-interval schedule. During a subsequent 10-min interval the lights were off and lever presses did not produce any reinforcement. Half of the rats received daily i.p. injections of 0.16 mg/kg lead acetate. The other half received saline injections. The injections were continued for 36 days. The dependent variable was the ratio of responses emitted during the "go" (light on) period to responses emitted during the "no go" (light off) period. The chronic effect of this treatment was a statistically significant increase in the day-to-day variability of performance observed in the treated group. The overall mean performance of the groups was not different. Since no blood-lead data were obtained and a questionable route of administration used, interpretation of the data is difficult. It is uncertain whether

variable behavior is a result of chronic lead exposure or possible reflection of variable uptake of lead from the injection site. However, the finding of a more variable behavior after toxin exposure is not an uncommon or insignificant finding in either man or animal models.

c. Zenick et al.[65]

Zenick et al.[65] have also examined the performance of lead-exposed rats on fixed-interval schedules of reinforcement. Female rats were exposed daily to 750 mg/kg of lead acetate via a restricted watering schedule for 70 to 80 days prior to mating. Exposure was continued throughout gestation and lactation. At weaning, one half of the lead-exposed offspring were weaned to the same lead-containing drinking water while the remaining half were weaned to normal tap water. This manipulation produced three groups of animals: those exposed throughout their life, those exposed only only during early development, and control animals. Beginning at 42 to 49 days of age offspring were tested on a fixed interval, 1-min schedule of reinforcement which lasted 45 min/day for 20 days. No effects were seen in those animals exposed to lead only during development. However, those rats on continuous exposure received significantly fewer reinforcements per session than controls even though they exhibited a normal scallop pattern of responding characteristic of fixed-interval schedules. The authors suggest that the continuously lead-exposed offspring may be more reactive to the test environment and therefore disengage from bar-pressing behavior to engage in exploratory behaviors. Although the developmentally exposed rats received the same number of reinforcements per session as did controls, their response rate per session was higher. Beyond the common finding of increased response rate under fixed-interval schedules of reinforcement, it is difficult to compare the study by Slechta[47] and Zenick et al.[65] since Zenick et al. used higher exposure levels and initiated lead exposure earlier in the animals' life.

d. Slechta[47,68]

Slechta[47,68] like Snowdon[19] and Shapiro et al.[67] chose to examine the effects of post-weaning lead exposure on subsequent behavior. Exposures to 50, 300, or 1000 ppm of lead acetate or tap water solutions were initiated in 37 20 to 22-day-old rats. These exposure levels had no effect on growth rate. The beginning of behavioral training was preceded by 35 days of lead exposure. Following 5 days of response shaping and 30 daily fixed-interval experimental sessions, the lead-acetate solutions of three subjects from the 50 ppm group were replaced with tap water. All subjects were subsequently tested for an additional 60 daily sessions. Blood-lead determinations were made at 150 days of age, i.e., after 125 days of chronic exposure.

The fixed-interval schedule of reinforcement used in this study was an FI-30 sec. On this schedule, the first response occurring after a 30-sec period elapses is reinforced by access to food. All other responses have no consequence. Response rates under this schedule generally increase as the interval progresses, reaching a maximum at 30 sec.

Several findings of particular interest were reported. First, a lead-induced behavioral alteration was demonstrated in postweaning animals, a finding which is at odds with most prior literature (see Table 1). Second, the lower two concentrations (50 and 300 ppm of lead acetate) appeared to increase the rate of responding approximately four times greater than controls while the highest exposure level decreased response rates slightly. Similar reports of a biphasic dose-response recently appeared.[45,48] Finally, the lead-induced behavioral changes dissipated over time. This latter finding suggested to Slechta a similarity to the disappearance of hyperactive behavior in children following the transition from adolescent to adult. Like Hastings et al.,[51] Van Gelder et al.,[44] and Shapiro et al.,[67] she also noted an increased intersubject variability in response to lead.

All data from treated animals were presented as a percent of their corresponding control group. Because of this procedure, it is not possible to compare the effects reported at 50 ppm against those attained at 300 ppm since any apparent difference may have been due to a difference between their respective control groups. It would have been helpful in this regard if an analysis of the three sets of control data had been provided. The 50 ppm exposure condition and behavioral assessment were replicated. The data provided indicate that the median performance scores, responses per minute, were essentially equivalent across replications for both the control and treated animals.

All data were analyzed using nonparametric procedures. Although it is not explicitly stated, this was probably due to the highly variable non-normal response distributions obtained both between subjects and across time.

The nature of the interaction between the time course of lead exposure and observed changes in performance during the same interval is complex. Even with about 35 days of exposure prior to the initiation of testing, peak behavioral changes were not seen until session 30 in the 50 ppm group and session 10 in the 300 ppm group. Then, despite continuing exposure, the treatment effects began to dissipate. After an additional 60 sessions the performance of lead-exposed rats approached control levels. Since blood-lead levels were not monitored during this period it is not possible to attribute this phenomenon to either a decreasing body burden of lead or a behavioral adaptation by the lead-exposed animals. Slechta and Thompson[68] suggest the former hypothesis and point to a decreasing rate of lead absorption as the rats attain adulthood. If so, then the reported blood-lead levels obtained at about 150 days of age, i.e., about 70 days after peak behavioral effects were observed, may be misleadingly low. In fact the mean blood leads are quite low: 5, 8, 26, and 42 $\mu g/d\ell$ for control, 50, 300, and 1000 ppm groups, respectively. However, the 50 ppm blood-lead values are comparable to those reported by Cahill et al.[69] wherein 180-day-old males, exposed to 50 ppm lead from conception, had blood-lead levels of $6 \pm 0.4\ \mu g/d\ell$.

Because of the potential significance of this study, it would be highly desirable to see a replication of the study wherein a more complete documentation of internal lead burden and hematopoietic response were obtained. These data could then be correlated on an individual animal basis with the onset and alteration of behavioral effects observed during continuous exposure and following abrupt termination of exposure.

e. Barthalmus et al.[19]

Barthalmus et al.[19] have recently explored the utility of using adult pigeons as a model system for examining the effects of lead exposure on behavioral performance. Pigeons were trained to peck a response key under a multiple FR 30, FI 5 min schedule of food presentation. When rates of responding stabilized, lead acetate (6.25, 12.5, and 25 mg/kg of body weight) or sodium acetate solutions were given daily by gastric intubation. Blood-lead concentrations were measured weekly by atomic absorption spectrometry, and responding under the multiple schedule was measured Monday through Friday. Control intubations of sodium acetate did not affect responding under either component of the schedule. The 25-mg/kg dose of lead decreased rates of responding after 3 to 10 days of administration and usually was lethal between 18 and 35 days. Post-mortem examination of the birds showed obvious esophageal dilatation, damage to the crop, weight loss, and subarachnoid hemorrhages. Administration of the 25-mg/kg dose was discontinued in some birds after responding had ceased. Responding gradually began to recover, but rates of responding remained low and variable under both components of the schedule for many days. Daily administration of the 12.5-mg/kg dose of lead caused one death, but no obvious signs of intoxication

occurred in the other birds. However, three of the four birds surviving daily 12.5-mg/kg doses of lead showed decreased rates of responding under both schedule components within 30 day days of the initial intubation. The 6.25 mg/kg dose of lead produced only small changes in rates of responding during 70 days of intubation. Blood-lead concentrations were very high (150 to 3740 μg/dl) during treatment with all doses of lead. The highly variable, nonsystemic behavioral changes which were observed with this model limit its utility as a useful tool for exploring issues of relevance to the human problem. Furthermore it is very difficult if not impossible to translate blood-lead concentrations observed in pigeons to any mammalian species. The blood-lead concentrations reported were 10 to 100 times higher than those reported in studies where lead was lethal to mice, rats, sheep, and monkeys. The pigeon's capacity to survive these high blood-lead concentrations may be associated with the nuclear inclusion bodies which Barthalmus et al.[19] identified in the erythrocytes. These lead-inclusion bodies in the nucleated erythrocytes of pigeons may account in part for the low correlation between blood-lead concentrations and behavior in some pigeons which was also observed.

f. Deitz et al.[70]

These investigators examined the interaction between age at exposure and age at testing on the performance of rats working for food reinforcement. Three groups of lead-exposed Long-Evans male rats and their littermate controls were studied. Two of these groups of rats (N = 6 and 7) were intubated daily from the 3rd to the 30th day after birth with 200 mg/kg lead acetate. They were tested at either 3 or 21 months of age. The third group (N = ?) was continously exposed to lead, i.e., during gestation, lactation, and postweaning. The pregnant and lactating dams were exposed to 250 ppm of lead in drinking water and the offspring were placed on this same solution at weaning. No blood-lead concentrations were reported for these animals at any stage of exposure. Therefore, it is not possible to evaluate the comparability of these different exposure protocols.

Behavioral evaluation consisted of a thorough examination of the performance of rats on a DRL schedule (Differential Reinforcement of Low response rates). Rats were reinforced for withholding a bar-press response for at least 20 sec. Dependent measures included response rate, total reinforcements received in a 60-min test session, percent of maximum possible reinforcements received, and number of responses emitted during the first 4 sec of the 20-sec interval inter-response times (IRTs) during which rats should withhold responding.

Deitz et al.[70] report that lead exposure increased the number of responses occurring during the first 4-sec interval. They suggested that lead may be producing a change in time perception or timing behavior as can be produced by alcohol or amphetamine. This effect was observed in all lead-exposed groups irrespective of exposure protocol or age at testing. However, it should be noted that the authors provide no statistical substantiation of their findings. The low number of subjects per group, individual variability of response, and inherent difficulties in statistical evaluation of operant data are the most likely reasons for reliance on descriptive rather than inferential statistical analysis.

The authors also reported on the influence of amphetamine and pentobarbital on the performance of these animals. They report that the effects of amphetamine (several doses were administered to each animal) were much more variable in lead-exposed rats than in their littermate controls. No lead-related effects were observed in the response of rats to pentobarbital, although aging shifted the dose-response curve to the left.

***g. Deitz et al.*[71]**

Deitz et al.,[71] like Barthalmus et al.,[19] chose to examine the effects of chronic lead exposure on the behavior of adult pigeons. Based on the findings of Barthalmus et al.,[19] they chose to use a dose of 6.25 mg/kg, i.e., the threshold dose for producing effects on schedule-controlled responding by pigeons. They also used the study as an opportunity to compare the relative sensitivity of an "acquisition paradigm" and a "performance paradigm". One half of the pigeons were required to learn a new solution to a problem (peck three keys in a predetermined order to get food) every session whereas the other half had the same problem every day. The pigeons were tested daily for 25 to 65 days prior to the administration of lead. Blood-lead levels prior to exposure were less than 5 $\mu g/d\ell$ and 101 to 340 $\mu g/d\ell$ within 7 days after intubations began. This exposure protocol increased the number of errors per session under the "performance schedule". Baseline performance was reported to be very stable. Of the four pigeons studied, one failed to demonstrate a statistically significant increase in error rates during lead administration, one showed an increasing error rate over 67 days and then began to recover over the next 99 days even though lead administration continued (cf. Slechta[47,68]), and another reached an error rate four times above pre-lead exposure rates before spontaneously beginning to recover. The remaining bird died suddenly without showing signs of gross toxicity.

In contrast to these birds, the four birds in the "acquisition schedule" had very unstable pre-exposure error rates. Therefore, it was not possible to detect any lead-induced increase in error rates. Furthermore, three of the four birds in this group unexplicably showed signs of gross toxicity. This may have been due to the very high blood-lead levels in the "acquisition group" (1360 to 2320 $\mu g/d\ell$). The authors conclude that behavior under the performance schedule appeared more sensitive to the effects of lead than behavior under the acquisition schedule or under the multiple schedule used by Barthalmus et al.[19] It remains to be seen whether the "performance schedule" would be the more sensitive in the more commonly employed lead-exposure paradigm wherein rats are exposed *in utero* and/or very early in life (thus preventing establishment of stable behavioral performance prior to exposure).

As noted in the preceding review of the work by Barthalmus et al.,[19] the usually high lead-binding capacity of the pigeon red blood cell makes it difficult to compare the threshold for behavioral effects seen in pigeons relative to that seen in other non-avian species. The reporting of other thresholds of toxicity, e.g., inhibition of heme synthesis, might assist in translation of these blood-lead values to a rodent or primate frame of reference.

5. Effects of Lead on Aggressive Behavior

Two reports in the literature in 1973 suggested that lead exposure produced an increased aggressiveness. Silbergeld and Goldberg reported that mice exposed to either 5 or 10 mg/mℓ of lead had a " . . . heightened frequency of fighting as determined by the incidence of bite frequencies observed on litter-mate males housed together."[72] Sauerhoff and Michaelson[73] also referred to an increased aggressiveness in lead-exposed rats during the fourth week of development. In neither report, however, was there an attempt to quantitate these observations of increased aggression.

***a. Hastings et al.*[51]**

Hastings et al.[51] exposed lactating rats to lead (0, 109, 545 ppm) from parturition to 21 days. This lead treatment produced no change in growth in the offspring. Individual pairs of male offspring (from the same treatment groups) were tested at 60 days of age for shock-elicited aggression. Lead-exposed groups showed significantly less

aggressive behavior than the control group. There were no significant differences among the groups in the flinch/jump thresholds to shock. This latter finding suggests that the differences seen in the shock-elicited aggression were not caused by differences in sensitivity to the shock stimulus.

b. Gray and Reiter[74]

Gray and Reiter[74] reported on the aggressive behavior of mice exposed to 5 mg/ml lead acetate from parturition. Aggressive behavior was measured by introducing an adult male intruder into the home cage of an individual experimental male. Control males wounded the intruder 85 times on the average during a 14-hr test period, while intruders to lead-treated and pair-fed male cages had means of 32 and 35, respectively. Therefore, the reduced aggressive behavior seen in these experiments cannot be explained by lead exposure alone, since similar reductions were observed in pair-fed controls. Nevertheless, in both the rat and the mouse, a quantitative examination of aggressive behavior suggests that lead exposure causes a decrease rather than an increase in aggressive behavior.

c. Cutler[75]

Cutler[75] examined the effects of lead on the social behavior of CFW mice. Dams were exposed to 0.1% lead acetate in their drinking water beginning at parturition and continuing throughout lactation. At weaning the offspring were continued on the same drinking solution. At 8 weeks of age, 40 males and 40 females, half treated and half controls, derived from a total of 30 litters, were evaluated for social behavior. Cutler[75] found a decrease in both the duration and frequency of social, sexual, and aggressive encounters between pairs of mice from the same treatment group relative to control pairs. Cutler found no treatment effects on growth, activity level, or occurrence of tremors.

d. Drew et al.[76]

The subjects in this study were 60 Long-Evans hooded rats. Lead exposure was limited to the lactation period. During this time the pups suckled dams who were ingesting food containing 0.1% lead acetate. No blood-lead data were reported. At 90 days of age, pairs of lead-exposed and pairs of control rats were tested for aggression induced by 5.0 mg/kg apomorphine. Latency to attack, total number of attacks, and total fighting time were recorded for a 60-min period which began 30 min after injection.

At some unspecified time following aggression testing, 12 lead-treated and 12 control rats were individually tested for apomorphine-induced stereotypy. Doses of apomorphine used were 2.5, 0.5, and 0.1 mg/kg or a vehicle control. Each animal received each dose in a counterbalanced order.

During aggression testing, lead-treated pairs were reportedly no different from control pairs following administration of vehicle alone. However, following apomorphine treatment lead-exposed rats showed an attenuated aggressive response on all three dependent measures relative to control rats. In marked contrast, no differences were reported in the incidence of apomorphine induced stereotypies.

The authors point out that apomorphine-induced aggression is thought to be mediated via the amygdala whereas apomorphine-induced stereotypy is thought to be mediated by the striatum and olfactory bulbs. This leads them to suggest that neonatal lead exposure may produce long-term changes in dopaminergic-functioning in the amygdala. This study supports the previously cited studies[50,74,75] in suggesting that neonatal lead exposure reduces aggressive behaviors in a very general fashion irrespective of species or testing paradigm.

E. Review of the Effects of Lead on Activity

Animal experiments designed to evaluate the behavioral consequences of lead-induced neurotoxicity have relied heavily on locomotor activity measurements. Table 4, which summarizes the studies on activity in lead-exposed animals, illustrates that considerable difference in experimental results has been reported. Differences in exposure (time, duration, level, route, etc.), species (rat, mouse, dog, monkey), and activity measurements (open field, shuttle box, residential maze, etc.) all contribute to these reported differences making the formation of a unified concept of the behavioral toxicity of lead difficult at best.

In an earlier section we reviewed the concept of activity, addressing some of the organismic and environmental factors which influence activity measurements. Now, we will review the reports of lead-induced changes in activity and finally we will present a possible unifying concept of the effect of lead on locomotor activity.

Since the initial description of lead encephalopathy in the rat by Pentschew and Garro,[1] considerable effort has been made to more closely define the extent of CNS involvement at subencephalopathic levels of lead exposure. This experimental effort has appropriately focused on the developing organism.

Much of the impetus for studying locomotor activity in animals exposed perinatally to lead comes from two sources. First, it is well documented that hyperactivity is one of the frequent neurobehavioral sequelae observed in children who survive episodes of acute encephalopathy resulting from high-level lead exposure,[96,97] A second, more cogent reason for studying locomotor activity is based on a report that children exposed to low to moderate levels of lead exhibited hyperactivity.[98,99] This report raised the serious concern that exposure to lead at levels compatible with environmental exposure may produce subtle alteration in behavior including hyperactivity.

In late 1973 and early 1974, two laboratories working independently and utilizing different species of laboratory animals, reported that early postnatal exposure to lead via the mother's milk resulted in elevated locomotor activity levels.[72,73] In both instances the magnitude of the effect of lead exposure on locomotor activity was considerable (140 to 190% of control for rats and 300 to 400% of control for mice). But as we shall see, reproducibility of results, applicability of these results to low-level lead exposure, and generalization both across species and to a general concept of hyperactivity are questionable.

Table 4 summarizes the reports on the effects of lead exposure on locomotor activity in laboratory animals. The pertinent data include species, exposure conditions, method of activity measurement, tissue levels of lead, nutritional status of the animal (when available), and the reported effects on activity.

Several critical questions will be addressed in this section. Does lead exposure alter locomotor activity? If so, what is the behavioral basis for this altered activity? And finally, are these changes reflective of subtle alterations in CNS function, relevant to environmental exposures or are they more reflective of postencephalopathic changes?

1. Locomotor Activity in Young Rats

a. Sauerhoff and Michaelson[73,77]

Using a modification of the Pentschew and Garro[1] exposure regimen, Sauerhoff and Michaelson[73] and Sauerhoff[77] exposed lactating female rats to 4% lead carbonate in the diet. On the 16th day postpartum, the concentration of lead in the diet was reduced to 40 ppm. Littermates were tested as a group at 25 to 28 days of age in a test cage similar to the home cage (Selective Activity Meter)®. These data were collected in four blocks of 3 hr during the light cycle and one block of 12 hr during the dark period extended over 4 days. Although they present data as counts per hour for a 24-hr period,

Table 4
EFFECTS OF LEAD EXPOSURE ON LOCOMOTOR ACTIVITY IN LABORATORY ANIMALS

Species	Exposure conditions	Lead concentration μg%		Test conditions, in order of presentations: 1. Method 2. Length of testing 3. Group size 4. Age	Nutritional status	Results	Ref.
		Blood	Brain				
Monkey (Rhesus)	0.5 mg Pb-acetate/kg/day in formula for 4 weeks	60—100	—	1. Observed locomotor activity	Normal	Hyperactivity (qualitative measures); no drug challenge	15
Rat (Bar F. Rabbitry)	35 mg/kg Pb to dams by gavage from parturition to 21 days			1. Photoactometer 2. 20 min 3. Individual 4. 49 days		Normal activity; no drug challenge	35
Mouse (Charles River, CD-1)	5 mg/kg Pb-acetate in maternal H_2O starting at parturition	—	—	1. Open field 2. 30 min; 2 sessions 3. Individual 4. 35 and 44 days	Undernourished	Hyperactive; no drug challenge	88
Rat (Simonsen)	10^{-4} and 10^{-2} *M* Pb-acetate in maternal H_2O from conception and in pup's H_2O after weaning	—	—	1. Open field 2. 2 min 3. Individual 4. 31 days	Undernourished	Hypoactive (61% of control); no drug challenge	45
Rat (Simonsen)	10^{-4} and 10^{-2} *M* Pb-acetate in maternal H_2O from conception and in pup's H_2O after weaning	10^{-4} M: x = 1.1±1.4 10^{-2} M: x = 0.2±0.1	— —	1. Open field 2. 5 min; 3 sessions 3. Individual 4. 30—32 days	Undernourished	Hyperactive (≈ 300% of control); no drug challenge	46
Rat (Long-Evans, Charles River)	0.02 and 0.10% Pb-acetate in maternal H_2O from parturition to 21 days	Control = 11±4 0.2 mg/ml = 29±5 1.0 mg/ml	—	1. Running wheel 2. 3 weeks 3. Individual 4. 30—51 days	Normal	Normal activity; no drug challenge	51

		= 42±4					
Rat (Long- Evans, Blue Spruce)	0.05—5.0% Pb-acetate in mother's chow from parturition until 21 days; continuted in offspring at 0.25—25 ppm in chow until 35 days	—	—	1. Shuttle box, activity wheel 2. 1 hr 3. Individual 4. 75—77 days; 90—93 days	Normal — 0.05% group undernourished in 0.05—5.0%	Hyperactivity in shuttle box (182% of control); normal in activity wheel; no drug challenge	81
Rat (Long- Evans, Blue Spruce)	0.1% Pb-acetate in mother's chow starting at parturition until day 18; 10 ppm in chow from day 18—21; 10 ppm in pup chow day 21—28	—	—	1. Open field 2. (10 min)	Normal	Normal activity	92
				1. Running wheel 2. (1 hr)		Normal activity	
				1. T-maze alternation 3. Individual 4. 38—45 days		Hypoactive; altered response to d-amphetamine	
Rat (ARC Sprague-Dawley)	0.83 g/kg/day Pb-acetate by gavage to dam from day 2 parturition until day 21—23	—	29 days: ≈ 40	1. Photoactivity cage (BRS/LVE) 2. 23.5 hr 3. Individual 4. 24—27 days	Normal	Normal activity; no drug challenge	79
	0.83 g/kg/day Pb-acetate by gavage to dam from day 2 parturition until day 9; 1.25 g/kg/day Pb-acetate from day 10 to 21	—	29 days: ≈ 35		Normal	Normal activity; no drug challenge	
Rabbit (New Zealand)	1 mg-Pb-nitrate/day dissolved in 1 mℓ unilac milk formula (100 mg/ mℓ H_2O) for 30 days	Day 2: 145 ± 27	25	1. Activity cage (Lehigh Valley #1487) 2. 20 min; 5 sessions 3. Individual 4. 2,5,10,15,20—25 days	Normal	Hyperactive	88
		Day 10: 154 ± 25	30				
		Day 15: 128 ± 21	—				
		Day 20: 215 ± 35	55				

Table 4 (continued)
EFFECTS OF LEAD EXPOSURE ON LOCOMOTOR ACTIVITY IN LABORATORY ANIMALS

Species	Exposure conditions	Lead concentration μg%		Test conditions, in order of presentations: 1. Method 2. Length of testing 3. Group size 4. Age	Nutritional status	Results	Ref.
		Blood	Brain				
Rat (Long- Evans, Charles River)	10,30,90 mg/kg/day Pb-acetate by gavage from 3—21 days of age	21 days 90 mg/kg = 226±21 35 days 90 mg/kg = 56±5	--	1. Jiggle platform 2. 4 days 3. Individual 4. 22—65 days	Normal	Hyperactive; no drug challenge	39
Mouse (Charles River, CD-1)	0.5% Pb-acetate in mothers H_2O from parturition until 21 days (weaning)	--	23 days: 190 350 days: 5	1. Vertically arrayed photoactivity cage 2. 3 hr 3. Individual 4. 141—161, 190—198, 211—219 days	Undernourished	Normal activity; altered response to d-amphetamine and apomorphine	48
	0.5% Pb-acetate in mothers H_2O from parturition until 21 days; 21 days and beyond in pups H_2O	—	23 days: 380 350 days: 180		Undernourished	Non-altered response to methylphenidate; non-altered response to phenobarbital	
	0.2% Pb-acetate in mothers H_2O from parturition until 21 days	21 days: 63.5	21 days: 24	1. Proximity counter; (Touch-plate) 2. 2—3 hr; multiple sessions 3. Individual 4. 22—23, 42—42, 62— 63, 110—134 days	Normal or heavier than controls	Normal activity; altered response to d-amphetamine	

	0.10% Pb-acetate in mothers H_2O from parturition until 21 days	21 days: 67.5	21 days: 36				
Rat (Sprague Dawley, Charles River)	5% Pb-carbonate in mother's chow from parturition to 16 days; 50 ppm in drinking water for remainder of experiment	—	—	1. Jiggle cage; residential maze 2. 4 min; 14 days 3. Individual; group of 3 4. 13—44, 120—160 days	Undernourished	Transient hyperactivity (200% of control at 13 days); normal at 44 days; normal levels in adults, but disrupted ultradian rhythms; altered response to d-amphetamine	78
Rat (Sprague Dawley, Blue Spruce)	5,50 ppm (≈ .01 and .001% Pb-acetate in H_2O) 40-day pretreatment of parents; continued from conception through adulthood	180-day males: 0 = 5±0.5 5 = 6±0.4 50 = 10±0.6	180-day males: 0 = 18±1 5 = 20±2 50 = 27±2	1. Residential maze 2. 5 days 3. Groups of 3 4. 120 days	Normal	Hypoactivity (53.78% of controls); altered response to d-amphetamine	9 69
Mouse (Charles River, CD-1)	5 mg/mℓ Pb-acetate in H_2O from parturition until 45 days	—	—	1. Residential maze 2. 2 days 3. Individual 4. 100 days	Undernourished	Normal activity altered response to d-amphetamine	
Rat (Sprague Dawley, CO)	4% Pb-carbonate in mother's chow from parturition to 16 days postpartum; 40 ppm in chow from day 17		29 days: 88±1.1	1. Selective activity meter 2. 24 hr 3. Groups of 6 4. 26—29, 50 days	Undernourished	Hyperactive at 29 days (140—190% of control); normal at 50 days; no drug challenge	73 77
Mouse (Charles River, CD-1)	2, 5, 10 mg/mℓ Pb-acetate in mother's H_2O starting at partuition	—	—	1. Proximity counter 2. 3 hr 3. Individual 4. 30—150 days	Undernourished	Hyperactive (300—400% of control); altered response to d-amphetamine, phenobarbitol, and methylphenidate	72, 83, 84

Table 4 (continued)
EFFECTS OF LEAD EXPOSURE ON LOCOMOTOR ACTIVITY IN LABORATORY ANIMALS

Species	Exposure conditions	Lead concentration μg%		Test conditions, in order of presentations: 1. Method 2. Length of testing 3. Group size 4. Age	Nutritional status	Results	Ref.
		Blood	Brain				
Rat (Sprague Dawley, Charles River)	8—91 mg/kg/Pb-acetate/day by gavage from 3—21 days of age	22 days: 81mg/kg = 71±12 35 days: 81 mg/kg = 23±1.4	—	1. Photoactometer 2. 30 min 3. Individual 4. 24—28 days	Normal	Normal activity; altered response to d-amphetamine	8, 59
Rat (Wistar)	1.38 g Pb-acetate/kg of chow (745 ppm Pb) for 60 days pretreatment to mother; continued in offspring from conception to testing	16 days: 26.6 190 days: 28.5	—	1. Open field 2. 3 min, on consecutive days 3. Individual 4. 90—140 days	Normal	Hyperactive (129% of control); no drug challenge	49

the data represent behavior attributable to multiple short-term exposures to the test environment and therefore are not comparable with data obtained by continuous sampling over a 24-hr period. They reported that the offspring of a lead-exposed mother exhibited elevated activity levels. Since only one group (N = 6 pups) was tested from each treatment, however, no statistical test can be applied to these data.

b. Reiter et al.[11] and Reiter[78]

Using a similar exposure regimen, Reiter[78] and Reiter et al.[11] exposed animals to 5% lead carbonate in the chow starting at parturition. On day 16, lead was removed from the diet and placed in the drinking water in a concentration of 50 ppm. Animals were repeatedly tested at various ages, beginning at 13 days of age, using a 4-min jiggle-platform measure of activity and stationary body movements. They reported an increased activity (200% of control) in 13-day-old animals. This elevated activity declined with age and returned to control levels by 44 days of age. Comparisons were made with pair-fed controls since this exposure resulted in a significant growth impairment. Whether this return to normal levels was caused by maturation or by repeated testing was not determined in this study. Animals were also tested as adults (120 days) in a residential maze, which allows continuous measurement of activity over extended periods of time. This test showed no differences in the activity levels as a result of treatment.

Sauerhoff[77] reported the blood-lead levels of suckling rats exposed to lead during the early postnatal period. When 4% lead carbonate in the diet of nursing mothers was replaced with 40 ppm Pb at day 16, the resulting blood-lead levels in the offspring were approximately 550 μg/dl. Because of the similarity in the experimental design between the Sauerhoff and Michaelson experiment and the Reiter study, blood-lead values (although not determined) were probably similar. Obviously 550 μg Pb per dl of blood represents extremely high-level lead exposure.

c. Overmann[39,60]

Overmann[39,60] exposed rat pups between 3 and 21 days of age directly to lead using daily gastric intubation in doses ranging from 10 to 90 mg/kg/day as lead acetate. Activity of 22- to 65-day-old rats was measured using a jiggle platform and was found to be elevated as a result of lead exposure. As in the Sauerhoff and Michaelson study,[73] animals were rotated between testing chambers over days and therefore the observed increase in activity reported by Overmann may be due to a lead-induced change in locomotor reactivity. Also, since there was no sex difference in locomotor activity reported in this study, it is likely that most behavioral testing was performed before the animals reached sexual maturity.

d. Sobotka and Cook[38]

Sobotka and Cook[38] also used gastric intubation to expose neonatal rats to lead acetate from 3 to 21 days of age. Each animal was given a daily dose of lead acetate which ranged from 9 to 81 mg Pb per kg/day. At 24 to 28 days of age locomotor activity was measured for 30 min using a photoactometer. They reported no difference in activity between control and lead-exposed animals. This finding is in contrast to the above report by Overmann who used a very similar exposure regimen. One striking difference between these two experiments was in the reported blood-lead levels. Whereas Sobotka and Cook[38] and Sobotka et al.[59] reported blood-lead levels of 71 μg/dl in 21- to 22-day-old rats receiving 81 mg/kg/day, Overmann[39] reports a value of 226 μg/dl for animals of the same age receiving 90 mg/kg/day. Therefore the higher internal exposure seen in Overmann's experiment may have accounted for the observed

activity changes. It is possible that other differences in experimental protocol, i.e., method of activity measurement, may have accounted for differences in this behavioral effect and that differences in blood-lead levels between experiments were due to differences in the analytical procedures used to measure lead.

e. Driscoll and Stegner[45]

Driscoll and Stegner[45] tested open-field behavior in 31-day-old rats exposed to lead from conception. Lead acetate was administered in the drinking water in a concentration of either 10^{-2} *M* (2.1 mg Pb per m*l*) or 10^{-4} *M* (.021 mg Pb per m*l*) with 10^{-4} *M* sodium acetate used for controls. Animals in the high-lead exposure group showed a significant reduction in 2-min open-field ambulation. However, this group also showed a significant reduction in growth. One possible explanation of the difference in the direction of the lead-induced change in the open-field activity as compared to the activity in the jiggle-platform experiments is the difference in the size of the test environment. If the basis for the behavioral change was related to a difference in the animals' reactivity to a novel environment, the large open field used by Driscoll and Stegner (1.3 m^2) could lead to a decreased activity in lead-exposed animals whereas with the smaller jiggle-platform apparatus the animals would show an increased activity. The difference in the response of the animals would then reflect a hyperactivity leading to species-specific freezing and reduced ambulation in the large open field.

In a second report, Driscoll and Stegner[46] were unable to verify the decrease in activity in open-field ambulation resulting from exposure to 10^{-2} *M* lead acetate. In this experiment animals were repeatedly tested in the open field for 5 min/day over 3 consecutive days. Statistical analysis indicated that the overall effects of lead were to increase ambulation. There was, in addition, a significant treatment-by-days interaction indicating that the fall in activity levels over days was greater in control animals. Therefore, animals in the high-lead exposure group (10^{-2} *M* lead acetate) had activity levels equal to control on day 1 but had elevated activity levels by day 3. This difference in habituation rates may be again due to differences in the reactivity of the lead-exposed animal to the test environment.

f. Krehbiel et al.[79]

Krehbiel et al.[79] exposed lactating rats to lead by gastric intubation beginning on day 2 postpartum through weaning (21 to 23 days). The two exposure levels of lead were 0.83 or 1.25 g lead acetate per kg body weight per day given in a split dose twice a day. Separate control groups were used for each lead group being pair-fed to match growth and intubated with vehicle. Activity levels of entire litters ($n = 6$ pups) were determined at 24 to 27 days of age using a photoactivity apparatus. In addition, at 28 to 29 days of age, the animals' activity during a 10-min observation period was scored for the frequency and duration of various motor items (i.e., locomotion, rearing, grooming, sniffing). Under these experimental conditions, no change in locomotor activity was seen measured either by photocell activity counts or by measurements of frequency and duration of various motor items. Brain-lead levels were determined to be 2.0, 1.7, and 1.0 μg/g dry weight for high lead, low lead, and controls, respectively. This is roughly equivalent to the brain levels reported by Sauerhoff and Michaelson[73] in their initial report on lead-induced hyperactivity. Krehbiel et al.[79] conclude that the lack of a behavioral effect was not due to a difference in internal exposure. In addition to the finding that lead exposure produced no change in short-term (30 min) activity, these authors reported normal levels of nocturnal and diurnal activity. Therefore, these data do not support the concept of lead-induced changes in locomotor activity.

***g. Hastings et al.*[50]**

Finally, Hastings et al.[50] reported on running-wheel activity of 30-day-old rats exposed to lead by suckling with mothers exposed to 1 mg/mℓ of lead acetate in the drinking water. This exposure resulted in blood-lead levels of 42 μg/dℓ at weaning, which are considerably below those reported by Sauerhoff and Michaelson (i.e., approximately 550 μg/dℓ). This experiment then represents moderate- to low-level exposure as contrasted to the Sauerhoff and Michaelson[73] study. Since animals normally show low levels of activity upon initial exposure to a running wheel, the effects of this lead exposure on reactive locomotor activity cannot adequately be tested. However, the control group showed a significant decline in activity over the first 3 hr while the lead-exposed group, starting at a lower level than controls, showed no significant change. Analysis of activity over the total test period (i.e., over 3 weeks of testing) revealed no significant treatment effect demonstrating that long-term running-wheel activity in 30-day-old rats was not affected.

2. Locomotor Activity in Adult Rats

At or about the time of sexual maturation, lead exposure has not been shown to reliably alter activity levels in the rat. As previously indicated, Sauerhoff and Michaelson[73] and Reiter et al.[11] found no differences in activity in lead-exposed animals tested between 44 and 50 days of age. These were animals which were reported to have increased activity at a younger age. Brown[35] also reported no differences in locomotor activity in animals tested at 49 days of age either in a photoactometer or in an open field.

Weinreich et al.[80] reported an increase in activity of 30-, 41-, and 52-day-old rats following dietary exposure to lead. At parturition, mothers were exposed to diet containing either 0, 0.5, 1.0, or 1.5% lead acetate. Offspring were continued on this diet following weaning. Activity, measured by a Selective Activity Meter, was reported to be elevated in all treatment groups. However, evaluation of these data is difficult since no information is provided regarding the number of litters employed, nutritional status of the offspring, size of litter, number of animals tested, and length of behavioral testing.

***a. Kostas et al.*[81]**

Kostas et al.[81] exposed lactating rats at parturition to lead acetate in the diet in a concentration of either 0.05, 0.5, or 5%. At 21 days of age, all concentrations of dietary lead were reduced by a factor of 1:2000 (0.25, 2.5, and 25 ppm) and lead was completely removed from the diet at 35 days of age. Two measurements of activity were employed using adult male subjects. Animals were tested at 75 to 77 days of age for 1 hr in a shuttle box activity cage and again at 90 to 93 days of age for 1 hr in a running wheel. Whereas lead exposure resulted in an elevated activity in the shuttle box, running-wheel activity showed no differences from control. This lack of sensitivity of the running wheel to lead-induced changes in activity is consistent with the findings of Hastings et al.[50].

***b. Winneke et al.*[49]**

Winneke et al.[49] also examined locomotor activity of adult rats using an open-field test. Females were exposed to either control or lead-containing diet (1.38 g lead acetate per kg diet) for 60 days prior to mating. Exposure was continued through the gestation and lactation period and discontinued at weaning. Offspring, therefore, received primarily indirect exposure to lead although some direct exposure certainly occurred between 16 and 21 days of age due to access of the rat pups to solid lead-containing food. The exposure resulted in blood-lead levels of 27 μg/dℓ and 28 μg/dℓ at 16 and

190 days, respectively (vs. control values of 2 μg/dℓ). These blood-lead values may be misleading due to the time at which these samples were collected. Peak lead levels would have occurred at or about weaning, reflecting access to solid lead-containing diet, yet these values were not reported.

This exposure regimen did not result in early undernutrition; in fact, lead-exposed offspring were reported to have significantly greater body weights. This finding is likely due to the reduced litter size of lead-exposed mothers (six pups per litter vs. eight pups per litter for controls) since fewer pups were competing for mother's milk.

When male offspring were tested as adults in an open field over 5 consecutive days, these investigators found an initial increase in activity on the first 3 days of testing. On days 4 and 5, activity of lead-exposed animals had returned to control levels. The authors concluded that this transient elevation in activity should be more appropriately called "lead-induced overreaction".

d. Reiter et al.[83]

Reiter et al.[83] also utilized an exposure regimen which provided for lead exposure prior to conception. In their experiment, both parents were exposed to lead-containing water for a period of 40 days prior to mating. Lead levels were 0, 5, and 50 ppm. Offspring were continually exposed throughout the experiment. Locomotor activity of adult males was measured in groups of three littermates tested in a residential maze over 4 days. This test system allowed for continuous (23 hr/day) measurement of locomotor activity which subdivided into exploratory, diurnal, and nocturnal activity. Exploratory activity (defined as the 1st hr of activity) was initially suppressed in lead-exposed animals, but this difference disappeared as the animals became established in the environment. In addition, they reported that nocturnal activity remained suppressed over the 4-day test period. However, the statistical method of analysis used by these authors (multiple t-tests) was inappropriate for their data set. When these data were re-analyzed, using an analysis of variance (ANOVA), the activity (exploratory and nocturnal) of lead-exposed animals was suppressed only on the 1st day of testing.

In a second study, Reiter et al.[11] reported no differences in residential maze activity of adult lead-treated rats. They speculated that the lack of a lead effect on locomotor activity in the second experiment may have been due to a different animal supplier. However, other differences in experimental protocol, i.e., differences in dose and period of exposure, may have accounted for the differences in activity.

The data reviewed here allow us to formulate a tentative working hypothesis regarding the effect of lead exposure on the rat. These data suggest that perinatal exposure to high levels of lead, resulting in internal exposures (i.e., blood lead) clinically associated with encephalopathy alters the animal's reactivity to a novel environment. In the young rat, this reactivity is increased by lead exposure, but this effect disappears as the animal matures. Exposure to lower levels of lead, more closely related to the environmental situation, does not produce this effect. In the adult animal, on the other hand, perinatal or lifetime exposure to lead results in a reduced reactivity.

As was previously indicated, the response of an animal to a novel environment depends on many factors both organismic and environmental. The test environments employed in the above studies vary considerably. If the test environment is stressful, a rat tends to freeze and ambulate less in that environment. Reducing an animal's reactivity may therefore result in increased activity. Marriott and Spencer[84] reported a biphasic dose-response relationship when rats were treated with minor tranquilizers (chlorodiazepoxide, meprobamate, or methylpentynol) and tested for locomotor activity in an open field. They found a consistent increase in activity at low doses followed by a decline in activity at high doses. This decline in activity at the higher doses was

well correlated with CNS depression and ataxia. Reducing the animal's reactivity with the administration of a minor tranquilizer therefore resulted in increased activity.

On the other hand, if one produces an increased reactivity in the rat, it may be expected that activity in an open field would be decreased. Reiter[78] reported that exposure to the pesticide Kepone®, which produces hyperexcitability in the rat, resulted in decreased ambulation in an open field. Therefore, in a test environment which is stressful, such as the open field, reducing the animal's reactivity (as with the administration of a minor tranquilizer) results in increased activity levels whereas increasing the animal's reactivity (as with Kepone® exposure) has the opposite effect.

However, the response of the animal to test environments of different size or complexity may differ considerably. For example, Reiter[78] also reported that Kepone® exposure resulted in an increased activity in a residential maze, suggesting that the intoxicated animals react differently to the two test environments. Animals with a treatment-induced increase in reactivity may therefore respond with elevated activity levels if the test environment is not stressful. This would explain the difference in the lead-induced change in reactivity in the various test environments (open field vs. jiggle cage or Selective Activity Meter®).

In the young animal, a lead-induced increase in reactivity may be expected to result in increased activity in some test environments (i.e., Selective Activity Meter® and jiggle cage) but a decreased activity in other test environments (i.e., open field). Conversely, the proposed decrease in reactivity in the adult animal would lead to an increased activity in some environments (open field and shuttle box) but a decreased activity in other test envronments (i.e., residential maze).

3. Locomotor Activity in the Mouse

a. Silbergeld and Golberg[72,83,84]

In the series of often-cited papers, Silbergeld and Goldberg[72,83,84] reported lead-induced hyperactivity in mice. Lactating females were exposed to lead acetate in the drinking water in concentrations of either 0, 2, 5, or 10 mg/m*l*. Direct exposure to the offspring was continued following weaning. Using a proximity counter to measure activity, they reported a 300 to 400% increase in locomotor activity that extended from 30 to 150 days of age in the offspring. It should be pointed out that a 300 to 400% increase in locomotor activity represents a substantial increase in an animal's level of ambulation. For example, Silbergeld and Goldberg's own data show that such an increase in activity is seen in normal mice given 5 to 10 mg/kg d-amphetamine and tested in this same apparatus. These are doses of amphetamine which produce obvious CNS stimulation which are apparent with even casual observation. Therefore, these reports of lead-induced hyperactivity were received with great interest, especially since the magnitude of the effect was so great.

Although these authors did not report the blood-lead levels of mice under these experimental conditions, Bornschein et al.[85] reported that under similar exposure conditions, 5 mg/m*l* lead acetate produces blood-lead levels of 190 μg/d*l* in suckling mice at 20 days of age. Again, this blood-lead value reflects a high internal exposure level.

One serious concern which is not unique to these studies deals with the growth retardation found in lead-exposed animals. As was previously indicated, early undernutrition has been shown to have a profound effect on behavior. For example, Castellano and Oliverio[86] reported that early undernutrition produces hyperactivity in mice. Therefore the hyperactivity reported by Silbergeld and Goldberg may have resulted from the undernutrition, independent of a lead effect. However, it is doubtful that these results can be explained solely on the basis of undernutrition. Castellano and Oliverio reported hyperactivity only in animals with severe undernutrition. Animals

showing a 60% reduction in body weight at 16 days of age showed hyperactivity when tested at 60 days of age whereas a 40% reduction in growth was without effect on activity. In the experiments of Silbergeld and Goldberg, a 30 to 40% reduction in growth was reported and therefore might have been expected to produce changes in locomotor activity. However, two additional differences in experimental design need mentioning. First, the method of producing growth retardation was different—large litter size vs. reduced food consumption of the lactating mother. Second, the apparatus used for activity measurements was different. Both of these factors add to the uncertainty of comparing these results directly and accentuate the need for adequate controls in lead toxicity studies.

Regardless of the influence of undernutrition on these results, a greater concern stems from the subsequent failure of two different laboratories[74,85] to replicate the findings of Silbergeld and Goldberg, using the same strain of mouse and the same exposure regimen.

b. Bornschein et al.[85]

Bornschein et al.[85] exposed lactating mice to 5 mg/mℓ of lead acetate and tested offspring in activity chambers identical to those employed by Silbergeld and Goldberg. They were unable to verify lead-induced hyperactivity in mice, even though undernutrition was also present in their animals. These investigators also examined the effect of undernutrition alone on locomotor activity. A large spectrum of growth rates was produced by raising mice in both normal size (8 pups) and large size (16 pups) litters. They reported a strong negative correlation between activity levels and body weights; i.e., the more undernourished the animal the higher its activity level. A subsequent report from this same laboratory[87] extended these observations. Mice were tested at 35 to 37 days of age in a proximity counter as previously reported. There was no overall effect of undernutrition on locomotor activity. However, the rate of change in activity over the 2-hr test period was significantly effected by undernutrition (treatment-by-time interaction) such that the undernourished animals habituated more slowly. A third report from this laboratory[48] again found no effect of lead exposure (5 mg/mℓ) on baseline activity of mice.

c. Domer and Llera[88]

Domer and Llera[88] using an exposure regimen similar to Silbergeld and Goldberg measured locomotor activity in mice at 35 days of age in an open field. Lack of detail in the description of the experimental design, i.e., number of litters, number of pups per litter, number and sex of animals tested, etc., makes interpretation of this experiment difficult. Although they report an increase in locomotor activity in the offspring, no statistical analysis of the data was presented. Examination of the activity data (1018 ± 40 vs. 1359 ± 209 for control and lead-exposed animals, respectively) suggests that these differences would not attain statistical significance (assuming eight animals per group and using the above values, a t-test indicates no significant difference). This report therefore sheds little light on the question of lead-induced hyperactivity in mice.

4. Locomotor Activity in Other Species

a. Lorenzo et al.[14]

Lorenzo et al.[14] examined locomotor activity in rabbit pups who were fed milk supplement containing lead nitrate. Animals were given 1 mg of lead nitrate per day and activity levels were measured at various ages during the first 25 days of age using a photoactometer. Although no significant group differences were found, nonparametric statistical analysis showed some differences in activity during the earlier portions of the 20-min test periods.

***b. Allen et al.*[15]**

Allen et al.[15] exposed infant rhesus monkeys to lead acetate (0.5 to 9 mg/kg) via their formula or by consumption of lead particles from lead-base surrogate mothers. Hyperactivity was reported in these animals, however, no quantitation of this behavior was performed and therefore caution must be exercised in any consideration of this report.

5. Drug Response of Lead-Exposed Mice

A number of different investigators, using both mice and rats, have evaluated the locomotor response of lead-treated animals to a variety of psychoactive drugs. Silbergeld and Goldberg [83,84] were first to study the response of lead-treated mice to various drugs which are used in the treatment and diagnosis of minimal brain dysfunction in children.

***a. Silbergeld and Goldberg*[83,84]**

In their initial study, Silbergeld and Goldberg[83,84] reported that lead-treated hyperactive mice responded paradoxically to the two stimulant drugs, amphetamine and methylphenidate. Data presented for amphetamine showed that lead-treated mice had activity levels below pre-drug baseline, whereas control animals showed the expected increase in locomotor activity. However, examination of the activity data following administration of methylphenidate raises questions as to the exact nature of the "paradoxical" response. Both control and lead-treated mice responded with increased locomotor activity following 40 mg/kg of methylphenidate; however the response of the lead-treated mice was markedly attenuated. Within 90 to 120 min animals were below their pre-drug level. This time course of the response would be expected if the lead-treated animals were entering into stereotypic behavior (a behavioral pattern characteristically seen following high doses of amphetamine-like compounds). Although the authors state that no stereotypic behavior occurred in lead-treated mice, no quantitation of this behavior was made. Furthermore, this stereotypic behavior has been observed in lead-treated mice by other investigators.[85] Inspection of the dose-response curve for amphetamine also indicates that at the lower doses of d-amphetamine (2 and 5 mg/kg), lead-treated mice responded with an increase in activity. In addition to this altered response to stimulant drugs, lead-treated mice were reported to have an increased locomotor activity following administration of phenobarbital (20 mg/kg) whereas control animals showed no locomotor response to this dose level.

Silbergeld and Goldberg [83] subsequently studied the locomotor response of control and lead-treated mice to a number of pharmacological agents including apomorphine, atropine, neostigmine, physostigmine, α-methyl-paratyrosine, benztropine, chlorpromazine, L-DOPA, fenfluramine, and 2-dimethyl-aminoethanol. Animals were exposed to lead at parturition via the mothers' drinking water as was previously described. A single exposure level of 5 mg/mℓ lead acetate was employed and offspring of both sexes were tested for their drug response between 40 and 90 days of age. With the exception of physostigmine, no dose-response data are presented but rather the response of animals following one dose of drug was reported.

The response of lead-treated mice was reported to be different from controls for all drugs except chlorpromazine and neostigmine. They concluded that "cholinergic antagonists and several aminergic agonists appear to exacerbate lead-induced hyperactivity while cholinergic agonists and aminergic antagonists appear to suppress this hyperactivity."[83] However these results are not without question. For example, apomorphine (10 mg/kg) was reported to produce increased activity in lead-treated mice. Yet, without subjecting these data to a 2-way ANOVA, this data appear equivocal. In fact,

no indication is given throughout the results section as to the methods employed for statistical analysis.

Without adequate dose-response data it is difficult to interpret much of these data. Since many of these drugs have dose-response functions which are either U-shaped or inverted U-shaped, it is difficult to determine the direction of change produced by lead exposure, that is, exactly where the single point falls of the dose-response curve. Again, the possible contribution of early undernutrition to these results must be considered. Bornschein et al.[85] and Loch et al.[87] found paradoxical lowering of activity in undernourished mice following doses of 10 mg/kg of d-amphetamine, but only during the 2nd hr following drug administration. In the 1st hr activity showed the expected increase, although to a lesser extent than in controls. These authors postulated that early undernutrition shifts the dose-response curve to the left such that animals given high levels of amphetamine (10 mg/kg) enter into stereotyped behavior sooner than controls, and that this behavior then prevents the occurrence and the recording of locomotor activity.

b. Gray and Reiter[74]

Gray and Reiter[74] also measured locomotor activity in lead-exposed (5 mg/ml from parturition until 45 days of age) and control adult male mice following administration of d-amphetamine. Again this exposure level was associated with early undernutrition. When tested as adults (100 days of age) lead-exposed animals showed an attenuated response to d-amphetamine. Pre-drug activity levels were not different from control.

c. Rafales et al.[48]

Rafales et al.[48] investigated the effects of both lead exposure and undernutrition on the locomotor response to drugs (amphetamine, methylphenidate, phenobarbital and apomorphine). Lead exposure was according to the method of Silbergeld and Goldberg and employed various levels of lead exposure ranging from 0.02 to 0.5% lead acetate in the drinking water.

In the first experiment, lactating mice were exposed at parturition to water containing 0.5% lead acetate. At weaning the lead-treatment group was subdivided with half the animals receiving lead-containing water and half the animals receiving tap water. These exposures resulted in a significant reduction growth. Adult animals were tested for their drug response using a photoactometer (modified version of a Motron Motility Meter®). Neither of the two durations of lead exposure had a significant effect on predrug activity levels.

Although the overall differences between the activity of lead-exposed and control mice in response to d-amphetamine failed to attain statistical significance, they observed a significant treatment-by-time interaction. The tendency was for neonatally exposed mice to have larger increases in activity and for continuously exposed animals to have smaller increases than controls. Methylphenidate (40 mg/kg) produced a similar locomotor response in both control and lead-exposed mice. Finally, apomorphine (4 mg/kg) produced a differential response in control and lead-exposed animals. Again no overall treatment effect was observed but a significant treatment-by-time interaction was observed. Continuously lead-exposed mice were more active than controls, and neonatally-exposed animals were less active than controls.

Rafales et al.[48] also reported on the locomotor activity and drug response of the offspring of animals exposed to either 0, 0.2, or 0.10% lead acetate. Exposure lasted from parturition until weaning at 21 days of age and produced no differences in growth of the offspring. Activity measured at 22 to 23, 42 to 43, and 62 to 63 days was not significantly affected by lead treatment.

Administration of 10 mg/kg d-amphetamine to mice at 42 to 43 days of age resulted in a significant treatment-by-time interaction with lead-exposed animals showing lower activity levels than control during the latter part of the test session. Animals were tested at 62 to 63 days of age for their locomotor response to 20 mg/kg of phenobarbital. No treatment-related differences in drug response were observed. Finally, animals were given various doses of d-amphetamine (2.5 to 10 mg/kg) at 110 to 134 days of age. At the 5.0 mg/kg dose there was a significant reduction in the amphetamine response due to treatment. At the 2.5 mg/kg dose a treatment-by-time interaction was again observed with lead-treated mice showing less activity than controls during the latter intervals of the test session.

What conclusion can be reached concerning the drug responsiveness of lead-exposed mice? There are considerable data which demonstrate that lead-exposed mice show an attenuated response to d-amphetamine. The results reported by many investigators are confounded by the presence of early undernutrition in the lead-exposed animals since this manipulation has also been shown to alter the drug response (Bornschein et al.,[85] Lock et al.[87]). Nevertheless, the findings of Rafales et al.[48] indicate that lead treatment in the absence of undernutrition results in an altered response to d-amphetamine. The nature of this altered response consists of an attenuation in the drug-induced locomotor activity which is most clearly present during the latter portion of the drug response.

The initial findings of Silbergeld and Goldberg[83,84] reporting an altered response to methylphenidate and phenobarbital were not verified by others. These discrepancies require further investigation.

6. Drug Response in Lead-Exposed Rats

a. Sobotka and Cook[38]

Sobotka and Cook[38] examined the locomotor response of control and lead-exposed rats to various doses of d-amphetamine. Animals exposed directly to lead (9 to 81 mg/kg/day) from 3 to 21 days of age were tested for their drug response between 24 and 28 days of age. Neonatal lead exposure to 81 mg/kg resulted in a significant reduction in the amphetamine response. Further, these animals showed normal growth during the developmental period.

b. Reiter et al.[91]

Reiter et al.[91] examined the effects of d-amphetamine administration in adult male rats exposed throughout lifetime to lead acetate (5 or 50 ppm) in the drinking water. This exposure had no effect on growth. Animals were given 4 mg/kg of d-amphetamine and locomotor activity was recorded in a residential maze. Lead-exposed animals showed an attenuated response to the drug which was related to the level of lead exposure. Unfortunately a dose-response to amphetamine was not determined.

In another series of experiments, Reiter et al.[91] exposed lactating rats to 5% lead carbonate in the diet from parturition until 16 days at which time lead was removed from the food and placed in the drinking water in a concentration of 50 ppm. Adult animals were then used to determine the dose-response relationship to amphetamine in control, lead-exposed and undernourished pair-fed controls. They found that undernutrition shifted the dose-response curve to the left (a finding which agrees with the data of Bornschein et al.[85] in the mouse). Lead exposure, on the other hand, shifted the dose-response curve to the right such that animals exposed to lead exhibited an attenuated drug response.

c. Kostas et al.[92]

The effects of d-amphetamine on several measures of activity and spontaneous al-

ternation were evaluated in control and lead-exposed rats.[92] At parturition, nursing mothers received either a control diet or a diet containing 0.1% lead acetate. After 28 days, dietary lead was reduced to 10 ppm. Animals were tested in an open field at 38 to 45 days of age following the administration of either 0, 1.5, or 3.0 mg/kg of d-amphetamine. In general, Kostas et al.[92] found lead exposure altered the amphetamine response although the exact effect depended on the particular behavioral measure. For example, differences were seen between control and lead-treated rats in grooming, center open-field activity, and percent of alternation following d-amphetamine administration. However, behaviors such as rearing and perimeter open-field activity were not different between treatment groups.

These data indicate that lead exposure has been shown to consistently alter the behavioral response of rats following administration of amphetamine. Whereas the occurrence of an attenuated drug response seems well documented, the occurrence of "paradoxical" response is questionable. Unfortunately, little or no work has been reported on the response of lead-exposed rats to other psychoactive drugs.

F. General Critique of Animal Studies

Clarification of the nature of the interaction between lead and behavior has been sought through the use of animals models. Unfortunately, much of the data generated by these animal studies are of little use due to inappropriate exposure levels or the lack of control over, and systematic variation of, critical independent variables known or suspected to interact with lead. However, one of the most damaging aspects of these animal studies has been a lack of a clinical perspective both in the definition of the critical issues and in the design of studies to deal with these issues.

Few animal studies adequately simulate the lead exposure conditions found in young children, either with respect to the levels of exposure or the timing of the exposure. There is often an inadequate or nonexistent history of lead exposure with respect to both the external and internal dose. Correlative measures of lead toxicity in other target systems, e.g., hematopoietic or renal indices, are generally absent. This makes it impossible to assess accurately the relative sensitivity of the major target organ systems in the lead-exposed animal. With respect to the general experimental designs, several design deficiencies frequently occur. These include (1) limited sample size or larger samples derived from a few litters (the latter permits genetic effects to have an inordinate influence on the results), (2) inappropriate application of statistical methods, and (3) confounding of variables, e.g., maternal undernutrition or neonatal growth retardation which results in an inability to determine specific causes for demonstrated effects. The selection of behavioral tasks is often made with little or no apparent rationale which would aid in the formulation and testing of hypotheses and interpretation of data. Finally, most investigators do not provide adequate documentation of the relative sensitivity of the behavioral tasks being used. This could be accomplished with the use of a standard reference compound. Since this has not been done, failure to observe a disruption in task acquisition or performance could be taken to mean that (1) the task is not sensitive enough to detect the deficit, or (2) the neural systems which mediate the behavior on that task are not affected by lead at the exposure levels examined.

Although "learning paradigms" are being used to demonstrate effects of lead on CNS function, the present data do not permit us to distinguish clearly between the effects of lead exposure on cognitive function (learning/memory) and effects on sensory-motor function, arousal, or motivation, which in turn can produce performance differences. Therefore, some of the studies in Table 3 appearing in the column headed "Acquisition" may in fact belong in the "Performance" column. This may be the

case in studies which report large group differences on the first day of acquisition. New studies specifically designed to test for this distinction must be conducted.

In spite of the extensive methodological differences and design inadequacies, several conclusions can be drawn from the data summarized in Tables 1 through 4. Learning tasks which use either positive or negative reinforcers appear to be equally sensitive to disruption following lead exposure. Therefore, lead exposure does not appear to have a selective effect on a specific motivational system.

Treatment effects are being reported both by investigators using manual testing procedures, which require a high degree of experimenter-subject interaction, and by those using automated apparatus requiring minimal experimenter-subject interaction. Hence, reports of significant treatment effects cannot be ascribed merely to experimenter bias. The effects appear to persist beyond the immediate exposure period, with behavioral disruption demonstrable in animals with blood-lead levels in the normal range at time of testing.

It is not yet clear whether the observed effects are direct effects of lead on the developing nervous system, or whether the effects are indirectly mediated through treatment-induced alterations in maternal behavior, maternal milk, or one of several potential peripheral target systems in the neonate. However, two recent studies[93,95] suggest that possible lead-induced alterations in maternal milk or maternal behavior are not serious concerns at low to moderate exposure levels. Several investigators have provided data that suggest that lead-induced behavioral alterations may not follow a classic monotonic function.[45,47,48]

Some types of learning problems appear to be more sensitive to lead-related disruptions than others. For example, passive avoidance acquisition and extinction are reportedly not sensitive to lead. Simple pattern discrimination is also apparently insensitive to lead exposure. Other forms of visual discrimination, such as size and brightness, appear to be particularly sensitive. In fact, reports of altered size discrimination may be special cases of brightness discrimination, since the different size stimuli (white pattern on a black background) also reflect different amounts of light. A recent paper[94] suggests that some of the learning/performance deficits reported in visual discrimination studies may be accounted for by a lead-induced impairment in scotopic vision brought about by impaired rod function. Further testing will be necessary to resolve this issue. Active avoidance tasks are also being used successfully to examine effects obtained following lead exposure. Both one-way avoidance and two-way shuttle avoidance tasks reflect a disruption in normal behavior. The one exception is a negative finding by Sobotka et al.[59] using a one-way avoidance task.

Deficits in task performance do not appear to be species-specific since they are being reported in rats, mice, dogs, sheep, and monkeys. Furthermore, recent studies suggest that behavioral alterations may be present in rats exposed to lead following weaning. These reports are contrary to the generally held opinion that adult or postweaning rats are insensitive to lead exposure. Still, since the number of reported studies using adult exposure protocols is quite limited, it is not possible to rule out the suggestion that these conflicting data merely reflect differences in task sensitivity. More research using adult exposure protocols and more sophisticated behavioral testing paradigms will be necessary to resolve the conflict.

In regard to studies of locomotor activity, the studies reviewed suggest that perinatal exposure to lead produces an increase in the animal's behavioral reactivity. If the test conditions are appropriate, this increase reactivity will be manifested as increased locomotor activity, although some text situations will show reduced activity. Therefore, the altered activity levels per se are merely reflective of a more basic nervous system dysfunction. Close scrutiny of the available data suggests that altered locomotor activ-

ity in young animals occurs only at moderately high exposure levels. It may be, then, that the changes in activity currently reported in laboratory animals are more representative of a postencephalopathic hyperactivity than of subclinical effects as has been suggested. On the other hand, the reactivity changes reported in older animals with lifetime exposure occur at much lower blood levels.

Finally, it has been suggested that neonatal lead exposure results in increased levels of aggression in adult rodents. The literature reviewed does not support this contention. In fact, the data suggest that lead exposure reduces aggression irrespective of the species or testing paradigm used.

Relevance of these animal data to the clinial situation and ease of interpretation of data can be increased in future studies by consideration of the following:

1. Better documentation of internal dosage levels is needed. Blood and tissue lead levels during exposure and at the time of testing are necessary.
2. Use of exposure protocols which do not produce growth retardation, or the use of experimental designs which permit an evaluation of the nature of the interaction between level of lead exposure and degree of growth retardation should be encouraged.
3. Increased number of litters should be included in each treatment group in order to reduce the contribution made by "litter effects". A second alternative would be to use a genetically more homogeneous test population.
4. Standard reference compounds (positive controls) or environmental manipulations which permit an evaluation of test sensitivity should be incorporated into the experimental design.
5. Inclusion of correlative indices of lead toxicity, e.g., free erythrocyte protoporphyrin levels in blood or ALA in the urine would aid in the extrapolation of animal data to humans.

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